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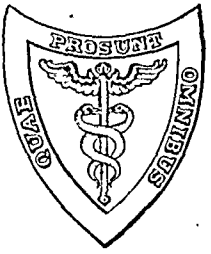
MEDICAL SCIENCES

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THE

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ORIGINAL ARTICLES.

MALIGNANT LYMPHOMA OF THE TONSIL.

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Malignant lymphoma of the tonsil occurs with sufficient frequency to merit careful attention and study, particularly as it is liable to run a rapid and fatal course. The initial symptoms are rather uniform but unless we be on our guard they may not lead us to suspect the serious nature of the condition. During the past 15 years there have been admitted to the Collis P. Huntington Memorial Hospital 236 patients suffering from malignant disease of the tonsil—of them 28 (11.8%) were proved by biopsy to be malignant lymphoma of one form or another. These statistics are in essential agreement with those of New and Childrey[1] who found 14.55% "lymphosarcoma" of the tonsil and nasopharynx among 357 cases of malignant disease originating in these regions. It should be noted, however, that their figures include tumors of the nasopharynx, while ours are strictly confined to those arising in the tonsillar region.

In this paper we present an analysis of these 28 cases, together with 9 others personally observed in either private practice or other hospital clinics.

The clinical course of malignant lymphoma of the tonsil varies markedly as the following histories indicate.

CASE 1.—A. B. (H. H. 33-307). This 65-year-old married Italian was admitted to the hospital on March 13, 1933. The past and family history were irrelevant. Three months before admission he noticed a painless lump in his throat on swallowing. He experienced no real inconvenience, however, until 2 months later when he began to have increasing difficulty in swallowing and raised from time to time considerable amounts of blood-streaked, purulent sputum. These symptoms increased steadily and for the 5 days prior to admission it had been virtually impossible for the patient to swallow at all. During his illness he had lost 35 pounds, presumably because of malnutrition consequent upon dysphagia. There were no other noteworthy symptoms.

Physical examination on admission revealed an emaciated man, occasionally raising a small amount of bloody sputum. There was moderate dyspnea. A firm, reddish, irregular, ulcerated, bleeding mass occupied the region of the right tonsil and extended beyond in the midline, pushing the uvula and soft palate before it. No enlarged lymph nodes were felt either in the neck or elsewhere. The physical examination was otherwise normal.

A portion of the tonsillar tumor was removed for microscopic examination. It (S-33-540) showed destruction of the normal lymph node architecture and a diffuse infiltration with large lymphocytes. Mitoses were moderately frequent. Diagnosis lymphocytoma.

The patient's respiratory distress grew rapidly worse and the day after entry a tracheotomy was performed and 600 R units of high voltage Roentgen-ray were given over the right side of the neck. The patient ran an irregular fever up to 104° F. and repeatedly coughed up large amounts of sanguinopurulent material. There developed dullness in the right back from the base of the lung to the spine of the scapula. Over this dull area there was diminished tactile and vocal fremitus and distant bronchial breathing. A chest tap revealed no pleural fluid. A Roentgen ray film of the chest showed "mottled dullness at base of right lung—probably pneumonia." The patient grew steadily worse and died on March 22, 1933, 3 months after his first symptoms, and 9 days after admission to the hospital. The autopsy (H. H. A-33-575) showed lymphocytoma of the right tonsil and bilateral pneumonia. There were no local or distant metastases from the original tumor. Death appeared to be due to an inhalation pneumonia. The case illustrates the great rapidity with which this disease may be fatal without obvious extension beyond the original site.

CASE 4.—H. R. (H. H. 26-1191), male 53, was admitted to the hospital on October 8, 1926 with the chief complaint of a swelling inside his throat. Two months before entry he noticed a small, painless lump in the region of his left tonsil. A reddish-gray membrane soon formed over it and the mass grew rapidly in size. A month later his voice became hoarse and he had occasional twinges of rather severe pain in his left ear and left temporal region. There had been no general symptoms, but during the past month swallowing had become increasingly difficult, and as a result he had eaten less and less. Since the onset of symptoms he had lost 12 pounds.

On admission, physical examination was essentially normal except for the presence of a firm, pinkish mass 4 cm. in diameter occupying the left tonsillar fossa. The tumor was covered with a grayish, sloughing membrane.

There were no lymph nodes palpable in the neck or elsewhere, nor were there found any other noteworthy abnormalities. Biopsy (S-26-2090) revealed it to be Hodgkin's disease.

Six seeds of 2 mc. each were inserted directly into the tumor. Three weeks later the mass was much smaller and 10 seeds, ½ mc. each, were placed in the remaining tissue. After 6 weeks the original tumor had entirely disappeared, but there was found an enlarged lymph node at the angle of the jaw measuring 3 by 4 cm. This was treated with high-voltage Roentgen ray. In January, 1927, 3 months after entrance to the hospital, his general condition seemed definitely worse. There were many small, firm lymph nodes in the left neck and he had occasional shooting pains to his left ear and temporal region. Radium in moderate dosage was applied externally over the enlarged nodes without beneficial effect. Both breathing and swallowing became increasingly difficult. The patient lost weight rapidly and, although no distant metastases could be detected, he died February 20, 1927, 6 months after his first symptoms had appeared. There was no autopsy.

CASE 12.—S. O. (H. H. 30-1180), a 67-year-old married woman, was admitted to the hospital on September 17, 1930. Her chief complaint was sore throat. For 2 months she had noticed a lump in her throat but it had given her no trouble until a month before entry when she began to have some pain on swallowing. A week later she noticed a mass in her right neck. There had been no other symptoms and the patient's general health was good. On entrance both tonsils were found to be enlarged. The right tonsil projected beyond the midline and presented an irregular, but non-ulcerated, surface. There was a firm, 1 cm. lymph node in the right submaxillary area and in both axillæ and both epitrochlear regions similar small lymph nodes could be felt. Otherwise physical examination showed no notable abnormalities. Both tonsils were removed with diathermy and the patient given high-voltage Roentgen ray to the cervical region. Examination of the excised tonsils (S-30-2462) showed them to be replaced by a lymphocytoma.

The patient responded well to treatment and in November, 1930, 2 months later, was entirely free of symptoms. The cervical lymph nodes had disappeared and there was no return of either tonsillar tumor.

In June, 1931, 8 months after admission, there was found on routine examination a firm, non-tender, rounded mass in the right flank about the level of the umbilicus. This was believed to be a mass of enlarged lymph nodes. There was no weight loss nor any symptoms. A month later, however, she noticed an enlarged lymph node in the right neck and experienced considerable pain in her right ear. High-voltage Roentgen ray treatments were given over the right neck. The cervical nodes responded well to treatment, but in July, 1931, a month later, she returned complaining of pain in the right upper quadrant. There was, at this time, no return of the tonsillar tumor but a lemon-sized mass could be definitely felt in the right upper quadrant and in each groin were several soft, non-tender lymph nodes. There had been a loss of 5 pounds.

There was a satisfactory response to Roentgen ray therapy to the posterior abdomen with a shrinkage of the enlarged nodes and a complete alleviation of the abdominal pain. In October, 1931, 3 months later, a considerable number of lymph nodes appeared in both sides of her neck, in both epitrochlear regions and in the left axilla and in each groin several large, firm, painless nodes were discovered. 1000 R units of Roentgen ray were given to the neck, 900 to each axilla and 900 to each groin. Two weeks later there was noted a most satisfactory response. All masses had decreased markedly in size and the patient felt considerably better. In November, 1931, a number of small shotty masses appeared subcutaneously in both upper eyelids. These were treated with radium with definite improvement.

From this time onward, however, the patient grew steadily worse. Large masses of lymph nodes appeared in the left groin resulting in marked edema of the corresponding leg. There developed considerable discomfort in the epigastrium and in spite of Roentgen ray therapy to the posterior abdomen, 900 R units, the patient died on January 8, 1932, 1 year and 4 months after her first symptoms were noticed. In contrast to the first 2 cases, the disease soon became very widespread, but it should be noted that the total duration of the disease was longer rather than shorter than in those patients whose symptoms and signs remained relatively localized.

Case 19.—D. L. (H. H. 30-582), a 73-year-old married woman, entered the hospital May 5, 1930, with the complaint of a "growth on the right neck." For 6 months she had noticed a gradually increasing growth in her right neck. Aside from an accompanying loss of strength, not inconsistent with her advancing age, she had no other symptoms. Examination at the time of admission revealed a well-nourished woman of 73. The right tonsil was markedly enlarged and extended beyond the midline. The tumor was pale pink in color, the surface smooth, and not ulcerated. In consistence the tumor was rubbery. The left tonsil appeared normal. Beneath the right mandible was a firm mass 5 by 3 cm. Examination of the tonsillar tumor (S-30-1229) showed it to be a lymphocytoma. High-voltage Roentgen ray in moderate dosage over the neck was instituted and within a month all nodes and the tonsillar tumor had disappeared. In December, 1930, 7 months after her admission, she was in excellent condition, but in February, 1931, in spite of the fact that she was symptom free, it was noted that the spleen, previously not enlarged, extended a few cm. below the umbilicus on inspiration. Seven hundred R units of Roentgen ray were given over the splenic area but no notable improvement ensued. The patient lost 10 pounds in spite of good appetite. The spleen did not diminish in size. There was no return of the tonsillar tumor, nor were there any lymph nodes palpable in the neck. Nine months later, the spleen was easily felt at the iliac crest, yet within the next 2 months, without any specific treatment whatever, it had receded beneath the ribs. The patient continued to feel as well as a person of her age normally would. In June, 1932, the spleen once more became palpable 3 cm. below the ribs and in each upper eyelid beneath the skin were found a number of small shot-like masses. There was moderate exophthalmos of the right eye. Radium was applied to the eyelids with excellent results and complete disappearance of the masses, but in August, 1932, the spleen had still further enlarged and was found to extend almost to the iliac crest once more. The patient continued to feel well but had lost 20 pounds. There had been no return of the local tonsillar tumor, nor any recurrence of the cervical nodes. When last seen 3½ years from her initial symptoms, she appeared to be in excellent health, although the spleen remained greatly enlarged.

Case 26.—G. B. (H. H. 19-668), a 54-year-old man, was first admitted to the hospital on August 20, 1919. His chief complaint was sore throat of several weeks' duration. There were no other symptoms. Examination revealed a pedunculated, ulcerated mass, the size of a small cherry, springing from the left tonsillar fossa. There were no other abnormalities on physical examination. The mass was excised and 7 seeds of 1 mc. each were inserted into the tonsillar fossa and the base of the tongue. The specimen (S-19-662) showed lymphocytoma. There was diffuse infiltration of the tissue with small lymphocytes. Mitoses were fairly frequent. So far as could be learned there was no recurrence of the tumor until August, 1932, 13 years later. At that time there was found to be a soft, ulcerated growth occupying the left tonsillar fossa and filling the entire nasopharynx. A second biopsy (S-32-1509) showed essentially the same picture as that seen 13 years before. Twenty-one hundred R units of Roentgen ray were

given over the cervical region and within 2 weeks the mass had entirely disappeared. A month later, however, the patient returned with marked ascites. The liver could be felt 3 cm. below the ribs. A large, soft nodule was felt in the rectum. Twelve hundred R units of Roentgen ray were given over the posterior abdomen with rapid diminution of the ascites. But 2 weeks later the patient seemed much weaker and a purplish red infiltrated area 8 cm. in diameter had appeared in the skin over the sternum. The patient grew steadily worse, hydrothorax developed, the ascites increased and the patient died on June 15, 1933, 13 years and 10 months after his original tumor was discovered and 10 months after the recurrence. The *autopsy* (S-33-1021) showed lymphosarcoma involving the cervical nodes, pancreas, gall bladder, pericardium, diaphragm, omentum, large intestine and ureters.

CASE 27.—E. K. (H. H. 21-1118), a married man of 46, entered the hospital on September 21, 1921, complaining of a recurrent growth in his throat. In 1918, he had had a painless tumor removed from the left tonsillar fossa. This proved to be a slowly growing plasmacytoma. A year later a similar mass was removed from the right tonsillar fossa. This also was a plasmacytoma. The patient was then free from symptoms until January, 1921, when he once more noted a mass in his throat. The tumor grew rapidly and soon caused some obstruction to swallowing.

In January, 1926, 8½ years after the removal of the first tumor, he complained of pain radiating down the outer side of his right leg. There were no signs of the original tumor. A Roentgen ray film of the lumbar and sacroiliac regions showed no abnormalities.

In March, 1926, there was a return of the tumor in the left tonsillar fossa and a few bean-sized lymph nodes were found in the neck.

In October, 1926, he complained of severe pain in the chest and a loose, troublesome cough. Roentgen ray examination of the chest showed for the first time, 8½ years after the initial tonsillar tumor, circular areas of diminished density throughout the ribs and pelvis, suggestive of multiple myeloma. Bence-Jones protein was found in the urine. He improved under Roentgen therapy but gradually a definite anemia developed, he became weaker and the cough, temporarily alleviated by Roentgen therapy, reappeared in an aggravated form. There was no return of the initial tonsillar tumor.

In October, 1928, he had a severe nosebleed for which no further cause could be found than a small ulceration on the septum. This bleeding continued intermittently until his death. The Roentgen ray findings at this time were typical of multiple myeloma, widely diffused throughout the flat bones. From this point onward the course was progressively downward and he died February 2, 1929, 10½ years after the removal of the first tumor. *Autopsy* (H. H. 29-338) showed multiple myeloma involving the ribs, radius and lumbar vertebræ, hypertrophy and dilatation of the heart, generalized arteriosclerosis and chronic nephritis. This case has been more fully described elsewhere.[2]

These case histories are representative of the various courses which the disease under consideration may run. It is apparent that like other forms of lymphoma the progress is extremely variable and unpredictable, although practically always downhill to death.

From a pathologic viewpoint (Table 1), among the 37 cases, reticulum-cell sarcoma was found 16 times, lymphocytoma 13, Hodgkin's disease 4, lymphosarcoma 2 and giant follicle and plasmacytoma each once. This proportion differs considerably from that in our entire series of malignant lymphoma, data upon which are

shortly to be published. Broadly speaking, Hodgkin's disease comprises some 40% of all lymphoma,* in contrast to a scant 10% among those arising in the tonsil. On the other hand, lymphocytoma and lymphosarcoma comprise but 30% in the general group and 43% in the tonsil group. While the tonsil series is, of course, small, it would appear that Hodgkin's disease arising in this region is rare and lymphocytoma and reticulum-cell sarcoma relatively common.

TABLE 1.—PATHOLOGIC TYPES.

	No. cases.	Age. Median.	Age. Extremes.	Median date of death (yrs.).	Alive after 10 yrs.
Reticulum-cell sarcoma	16	56.6	20–83	1.0†	0
Lymphocytoma	13	57.1	12–72	1.6‡	3
Lymphosarcoma	2	17.0	. . .	0.4	0
Hodgkin's disease	4	53.5	41–79	1.6	0
Plasmoma	1	43.0	. .	10.6	1
Giant follicle	1	67.0	. .	1.4	0

The age distribution (Table 2), shows that the peak incidence occurred in the 7th decade and that 62% occur between the ages of 40 and 69. The disease is rare in the 3d and 4th decade. Children under 10 are seldom admitted to the hospital, from which these

TABLE 2.—AGE INCIDENCE.

0–9	0	50–59	7
10–19	5	60–69	10
20–29	1	70–79	5
30–39	2	80–89	1
40–49	6		

data were largely obtained, and our statistics should, therefore, not be construed as indicating that the disease does not occur in this age group. The age distribution of the various types of lymphoma showed wide variations. The median age for each major group was approximately the same, namely, reticulum-cell sarcoma 56.6, lymphocytoma 57.1, Hodgkin's disease 53.5. But while reticulum-cell sarcoma was found to be quite evenly distributed from 20 to 83 years of age, lymphocytoma was not found in the 3d and 4th decades, the greatest number occurring between 10 and 20 and again between 50 and 72 years. The 4 Hodgkin's cases were all over 40 years. As would be expected both rapidly advancing lymphosarcomas were found in the second decade and the single case of plasmoma in the fifth decade.

* The inclusion of Hodgkin's disease as a lymphoma is not acceptable to many authorities. It is suggested that it be recognized as a member of the group of lymphomatoid diseases. (See J. Am. Med. Assn., in press.) Editor.

† One patient died of recurrence 9.3 years after the initial tumor; 1 was alive and well 7.4 years after the initial tumor.

‡ One patient died of recurrence 13.5 years after the initial tumor; 2 were alive and well 11 and 18 years, respectively, after the initial tumor.

Of the entire series 21 (56.8%) were males; 16 (43.2%) were females. New and Childrey found that 75% of their "lymphosarcomas" were males.

TABLE 3.—FIRST SYMPTOM.

Sore throat	14
Swelling of tonsil	6
Swelling of neck	11
Dysphagia	4
Deafness	1
Bloody sputum	1

The first symptoms noted by the patients were comparatively few in number. From Table 3 it may be seen that sore throat, often of weeks' duration, was the commonest symptom, while a "lump" in the throat or in the neck were the next most common. Dysphagia was the first symptom in 4 cases. Thus, 65% of the first symptoms might properly be directly referred to the throat. Any sore throat of considerable duration should, therefore, cause the practitioner to consider the possibility of lymphoma with serious consequences to come.

In general it may be said that the symptomatology of the various pathologic types does differ to a certain extent. Thus 11 of the 16 patients with reticulum-cell sarcoma complained of pain, while but 2 of the 13 with lymphocytoma had pain of any moment. This is in accord with the symptomatology which we have found in the lymphoma group as a whole. Reticulum-cell sarcoma is probably the most painful form of lymphoma of the tonsil. It is doubtful, however, whether one could make a differential diagnosis between the various types of lymphoma on the basis of physical signs and symptoms alone. Indeed, it is questionable whether lymphoma of the tonsil can be surely differentiated from carcinoma without biopsy.

That in the early stages the disease advances apace is apparent from the fact that while on the average patients reported to the clinic within 4 months from the time they were first troubled, yet on admission several new symptoms had appeared and the incidence of such symptoms as had been noted initially was markedly increased (Table 4). Lymph nodes in the neck, complained of as a first symptom in but 11 cases, had become sufficiently prominent to be noticed by the patient on admission in 22 instances. In a similar manner, while dysphagia was the first symptom noted in but 4 cases, it was a prominent complaint in 9 instances at the time of admission to the hospital, at which time fatigue was complained of by 4 patients. Five patients had already lost weight. In view of the prognostic import of local and distant metastases (a subject referred to in detail later) this rapidity of advance of the disease early in its course should constantly be borne in mind.

TABLE 4.—SYMPTOMS ON ENTRANCE.

Sore throat	17
Swelling of tonsil	13
Swelling of neck	22
Dysphagia	9
Deafness	3
Bloody sputum	3
Fatigue	4
Hoarseness	3
Loss of weight	5

The tumor was accurately described in 31 cases. It invariably occupied the tonsillar fossa, was always notably enlarged and often extended beyond the midline, pushing the uvula and soft palate before it and causing in 9 cases dysphagia of greater or less degree. In consistence, the tumor was rubbery, firm or hard in all but 2 cases, in which it was soft and friable. The mass was definitely ulcerated in 12 instances. In the remainder the tumor was smooth or slightly irregular but definitely not ulcerated; in but 1 (Case 26) was there a pedicle. The tumor in this case was excised and 7 gold seeds, 1 mc. each, inserted into the base of the mass. The tumor reappeared at the same site 13 years later. It is possible that in this instance the recurrence was in reality a second and entirely independent tumor. In general, the color of the mass was described as pink or opalescent and in 6 cases there was definite membrane covering its surface.

TABLE 5.—PROGNOSIS OF GROUP AS A WHOLE.

Patients living = 8 Average life = 5.5 yrs.		Patients dead = 29 Average life = 2.5 yrs.	
Well	Yrs.	Well	Yrs.
3	1	1	5
1	2	2	10
1	5		
2	10		
1	18		

The prognosis of the group as a whole is, of course, bad (Table 5). Only 1 of the series (Case 27, H. H. 18-406) appears to be cured, as he is free from signs and symptoms now, 18 years after the appearance of the initial tumor. Of the 8 patients alive at the present time (July, 1935), but 4 have survived the 5-year period. The average duration of life among those who succumbed to the disease was 2.5 years, but it should be noted that 2 patients survived 10 years yet died of a recurrence of their original disease; so that contrary to the rule in certain other malignant tumors, a very prolonged period of freedom from signs and symptoms must ensue before one can be certain that an actual cure has resulted.

At the time of admission to the hospital 12 patients had neither local nor distant metastases, 17 had enlarged lymph nodes in the neck and only 8 had generalized lymphadenopathy. Thus, in over 67% of the cases metastases had already occurred when the patient was first seen. This is in general agreement with the findings of

New and Childrey. In their series, 59% had cervical glands when first seen.

As is to be expected the presence or absence of metastases at the time of treatment appeared to have a definite relation to the duration of the disease. Thus, 42% of those patients who showed neither local nor distant lymph nodes lived over 3 years and 25% lived more than 10 years. The average duration to death in this group was 5.3 years, and 2 of this group died of unrelated diseases, 1 of cardiac decompensation and 1 of cancer of the cervix. On the other hand, but 33% of those who had local cervical metastases lived over 3 years and but 1 lived over 5 years. The average duration to death in this group was 1.7 years and, further, it should be added that 1 died of coronary thrombosis and 1 of tertiary syphilis. Those with generalized or distant lymphadenopathy fared still worse. The average duration of life in this group was 1 year. No patient in this group lived more than $2\frac{1}{2}$ years. It can be said, therefore, that the more general the involvement the worse the prognosis. That other factors enter in, however, is attested to by the fact that of the 12 patients who had no cervical or distant metastases at the time of treatment, 4 died in less than 1 year from the first appearance of symptoms. In 1 instance death was due to intercurrent pneumonia, directly traceable to the oral lesion. In the other 2, death appeared to be brought about by the dysphagia and pain of a very malignant and radiosensitive tumor. As in other forms of lymphoma there is great difficulty in predicting at the onset the subsequent course of the disease.

There would appear to be little difference in the prognosis among the various pathologic types. The median date of death in each major group was approximately the same—less than $1\frac{1}{2}$ years. It is to be noted, however (Table 1), that 1 patient with reticulum-cell sarcoma died of recurrence 9.3 years after the initial tumor and that 1 was alive, although still presenting evidence of the disease, over 7 years after the first symptom. In a similar manner, although the median date of death among the lymphocytoma group was 1.6 years, 1 patient died of a recurrence after 13 years, and 2 patients were alive and well 11 and 18 years respectively after the onset of the condition. It can thus be seen that too sweeping generalities must not be applied to the individual case.

The number of mitoses per oil-immersion field gave, in a general way, some indication of the prognosis. Thus those tumors which showed 10 mitoses per oil-immersion field were fatal in less than 6 months; those which showed but 5 were fatal on the average in $1\frac{1}{2}$ years; those which showed but 1 mitosis or less caused death in 3 years or over. Sufficient exceptions to these rules were found, however, to render it unsafe to be dogmatic as to prognosis on the basis of mitoses alone.

The treatment given was so varied as to be impossible to summarize. Nor can it be said on the basis of the data on hand that

one type of treatment seemed more effective than another. In general, during the earlier years (1919–1925) gold seeds numbering 4 to 12 and containing 1 mc. were inserted into the tumor and an additional dose of radium was given over the affected lymph nodes. In later years, seeds were occasionally used and the patient in addition was given successive high-voltage (220 Kv.) Roentgen ray treatments amounting to from 600 to 800 R. Local recurrence and distant metastases were treated alike and radiation in similar rather moderate dosage was given as metastases occurred.

In almost all instances the original mass responded well to treatment. This initial radiosensitivity, we believe, is most deceptive and in the light of the very early recurrence in the majority of instances we would now advocate heavier dosage as in the case of carcinoma. In 17 instances the response was regarded as excellent; that is, the original tumor and local lymph nodes, if any, disappeared completely in the course of 1 or 3 weeks. In 8 cases the response was fair, in 3 poor and in 2, (Cases 25 and 10), there was no visible effect on the tumor. The first of these latter patients lived 14 months, the second but 4 months.

In general, it may be said that the better the original response the greater the likelihood of the patient surviving a relatively long period of time. But that this rule is not invariable is shown by the fact that 1 patient (Case 14), whose response to his initial treatment was regarded as excellent, died with cachexia, dysphagia and severe pain 5 months later, and another (Case 17), whose initial response was poor, was still alive 2 years and 4 months later. In spite of the relatively favorable response in the vast majority of instances, local recurrence took place rapidly in most cases, on the average in 4.5 months. In 38% of the cases local recurrence was noted in less than 3 months, and in 67% of those patients who ultimately had distant metastases they were first noted within 9 months from the first treatment.

As has been said, local recurrence is common but in 44% of those who died there was no spread beyond the pharynx, nasopharynx and cervical nodes. Death in these instances is to be attributed to the dysphagia and to the attendant pain which in some instances was very severe, requiring the constant administration of opiates. In 2 instances (Cases 15 and 25), there developed a Horner's syndrome and in one of these (Case 25) there were repeated attacks of vomiting, bradycardia, exophthalmos and fainting. These attacks became more frequent and of longer duration. The patient finally died in syncope. In 56% of the patients who died the disease became generalized. Distant lymph nodes, the spleen and liver were frequently involved. One case developed classical acute lymphatic leukemia. Any or all organs may be involved in the process and the disease then takes on the characteristics of generalized lymphoma and must be treated as such. In 3 cases there was widespread nodular involvement of the skin. In Case 27, already

summarized above, a plasmacytoma of the tonsil metastasized 8 years later to the osseous system and the patient died with the classical symptoms of multiple myeloma.

Summary. 1. In 15 years there have been admitted to the Huntington Hospital 236 cases of malignant disease of the tonsil. Of these 28 (11.8%) were proven to be malignant lymphoma of one type or another.

2. The most prominent symptoms initially noted by the patients were persistent sore throat, swelling within the throat and enlargement of the cervical lymph nodes.

3. Of these patients 56% developed generalized lymphoma.

4. The excellence or rapidity of the immediate response to radiation is no index of the ultimate outcome.

5. The average duration of life from the onset to death was 2.6 years, the median 1.4 years, and the extremes were 3 months and 13 years.

6. One patient was alive 5 years, 2 10 years and 1 alive and free from symptoms 18 years after the onset.

7. The absence of local lymph nodes at the time of treatment is, in general, of good prognostic import.

8. Lymphoma of the tonsil should be regarded as but one type of malignant lymphoma and the ultimate widespread involvement seen in many patients must constantly be borne in mind.

9. It is suggested that those patients be treated as if they had carcinoma of the tonsil; that is, with very heavy initial radiation with comparable doses for recurrences.

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I. IRON AND ITS UTILIZATION IN EXPERIMENTAL ANEMIA.*

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It would seem that the reaction of iron in anemia should be delightfully simple and direct. There is a lack of iron and when

* We are indebted to Dr. David Loeser, of the Loeser Laboratory, for a liberal supply of colloidal iron for intravenous use.

absorbed or injected it should go directly into upbuilding of the large hemoglobin molecule which thereupon is incorporated into the red cell. The reasons why the reaction is so often confusing, unexpected and difficult of explanation are subject to debate, but one may at least suspect[2] that iron is concerned in the complex reaction within organ cells between various organs and comprehending body fluids—a reaction we name internal metabolism.

A monument erected to commemorate developments in iron metabolism would be, indeed, a Tower of Babel. Voices would be raised to convince us that metallic, reduced or inorganic iron is utilized differently and less effectively than organic or food iron. Again claims are put forward that ferrous iron[7] is utilized to greater advantage than ferric iron. Some investigators believe that copper is necessary for the utilization of iron.[3] Others believe that much more iron is taken into the body from the intestine than is utilized and that much of this is excreted as a surplus *via* the large bowel. Iron balance experiments, of course, do not tell us whether some of the iron is taken into the body and then eliminated in the feces, as it all may go through the intestine and escape in the feces.

Many different types of anemia have been studied. Human anemias obviously are complicated by innumerable variables which may confuse the picture. Experimental anemia due to food deficiencies in rats has been much studied by Myers and associates,[1] by Hart, Steenbock, Elvehjem and associates.[3,4] Other investigators have used anemias due to blood destruction or blood withdrawal. Some of the confusion in this voluminous literature is due to an attempt to apply findings in one type of anemia to a totally different type of anemia. Some related papers have been covered in an earlier report.[11]

Experiments with iron feeding are unsatisfactory in many respects whether the iron is contained within the food or given as a soluble salt, as there is no accurate measure of *iron absorption*. It is conceivable that the absorption of iron may be profoundly influenced by simultaneous food intake, digestive activity and bile factors or the actual need for iron within the body. Study of the feces gives us no help, as some of the iron may go into the body and subsequently be eliminated *via* the large bowel in the feces. Evidence is accumulating to indicate that many slight disturbances of internal metabolism may modify the utilization of iron to make new hemoglobin in experimental anemia in the dog, due to blood withdrawal.

It is not appropriate to discuss the therapy of human anemias but we wish to refer to an excellent paper by Heath, Strauss and Castle.[5] Much of the recent literature of hypochromic anemia is reviewed there. Iron administered parenterally, they state, gives a production of new hemoglobin which corresponds closely to a quantitative return. Their observations on human cases, therefore,

are in accord with the observations in simple experimental anemia given below.

When one gives iron intravenously in an experiment there is certainty that the iron, at least for a time, is within the circulation and body tissues. By no other means can one be sure of a given amount of iron gaining access to the internal body metabolism and estimates relating to Fe absorbed from the intestine are always indirect and give ample opportunity for debate and doubt. Our last report[11] dealing with iron feeding experiments was unsatisfactory to us because of the uncertainty relating to iron absorption.

For this reason we used intravenous iron, but this does not imply our belief that in human anemia this type of therapy is best. In certain types of human anemia where abnormalities of the intestinal tract may impair absorption, intravenous iron may be helpful but it should always be used with caution.

Methods. The routine care of these anemic dogs has been described in earlier publications[9,11]—also the preparation of the standard salmon bread which contains wheat flour, potato starch, cane sugar, canned salmon and tomato, cod-liver oil, yeast and a salt mixture. The iron content of this bread as used is 4.68 mg. per 100 gm.—the average of many analyses.

Net figures for hemoglobin production are given in all tables—for example, if a given dog produces 7 gm. of new hemoglobin per week during long bread control periods of 8 to 12 weeks and during iron feeding produces a total of 85 gm. hemoglobin during a 5-week period, we deduct 35 gm. for the basal bread output, leaving 50 gm. which are credited to the iron feeding. The iron feeding usually occupies a 2-week period with at least 3 weeks' after-period to include the "carry over" of surplus hemoglobin output which follows the Fe feeding period (compare Table 1).

The hemoglobin level in the blood by means of blood withdrawal is kept as constant as possible usually within 5% of the anemia level of 45% (100% = 13.8 gm. hemoglobin). If the anemia level at the start is 47% hemoglobin and at the end of the test period is 43%, we deduct 4 gm. hemoglobin from the total output to adjust the level to the original 47%. In these dogs a change of 1% hemoglobin reading is equivalent to a little more than 1 gm. hemoglobin in circulation at this anemia level.

Various iron salts have been used in these and other experiments, and Table 3 gives some illustrative experiments. These iron salts are fed mixed with the salmon bread, but the potency is related to the amount of Fe in any given salt or mixture.

Intravenous iron may cause serious trouble and even death if used carelessly or if the material is not properly prepared. We are indebted to Dr. David Loeser, of the Loeser Laboratory, for a liberal supply of $Fe(OH)_3$ in colloidal solution, which in these experiments has never given any untoward effects even when given in large amounts (Table 5).

Experimental Observations. We would emphasize the fact that these dogs which are subjects for iron therapy are in an excellent state of nutrition and activity in spite of a relatively severe anemia with a hemoglobin level of 40 to 50%, as compared with the normal level for these dogs of 130 to 150% hemoglobin, where 100% is equivalent to 13.8 gm. hemoglobin. The anemia level is maintained as nearly constant as possible by blood withdrawal and the removed

hemoglobin is credited to that particular week. Presumably the stimulus for hemoglobin and red cell production is a sustained maximum, but the appetite is unimpaired and intestinal absorption is normal. These dogs remain clinically normal and in weight equilibrium for years and many animals have continuous anemia histories for 8 to 12 years. These dogs would seem to be ideal subjects for the experiments dealing with iron absorption and utilization in anemia due to blood withdrawal.

TABLE 1.—IRON BY MOUTH IN OPTIMUM AND LARGE DOSES. LIVER PLUS IRON SUMMATION EFFECT.

Dog 30-117.

Diet periods, 1 week each. Food, grams per day.	Food cons., %.	Wt., kg.	Plasma vol., cc.	R.B.C., mil.	Blood Hb. level, %.	Hb. remov. bled, gm.
Fe, 40 mg.; br., 450; salm., 100; Kl., 40	100	14.1	910	5.3	48	36.2
Fe, 40 mg.; br., 450; salm., 100; Kl., 40	100	14.2	947	4.9	58	19.6
Bread, 450; salm., 100; Kl., 40 . . .	100	14.4	944	5.0	61	20.0
Bread, 450; salm., 100; Kl., 40 . .	100	14.1	896	4.9	49	21.8
Basal output, 10 gm. Hb. per wk. Total netHb. output			=	60 gm.	Total	= 98
Fe, 400 mg.; br., 450; salm., 100; Kl., 40	100	14.9	886	7.0	73	44.8
Fe, 400 mg.; br., 450; salm., 100; Kl., 40	100	14.9	864	6.2	58	54.4
Bread, 450; salm., 100; Kl., 40 . .	100	15.0	909	5.1	57	14.2
Bread, 450; salm., 100; Kl., 40 . .	100	15.4	960	4.6	68	13.4
Bread, 450; salm., 100; Kl., 40 . .	100	15.4	893	4.6	50	10.3
Total netHb. output			=	87 gm.	Total	= 137
Fe, 400 mg.; p. liver, 300; br., 300 .	100	13.9	842	6.4	64	60.5
Fe, 400 mg.; p. liver, 300; br., 300 .	100	13.9	852	5.8	61	41.3
Bread, 450; salm., 100; Kl., 40 . .	100	14.2	861	6.0	51	58.5
Bread, 450; salm., 100; Kl., 40 . .	100	14.3	864	4.6	57	21.8
Bread, 450; salm., 100; Kl., 40 . .	100	14.8	936	4.5	45	24 0
Liver control = 99 gm. Hb. Total netHb. output			=	156 gm.	Total	= 206

Br. = salmon bread; salm. = canned salmon; Kl. = milk powder (Klim).
Fe given as ferric citrate.

Table 1 gives three separate experiments done upon the same dog and we observe that the food consumption is 100% throughout; the body weight is subject to slight fluctuations and the plasma volume is relatively constant even in the face of heavy blood withdrawal. This dog during long control periods put out 10 gm. hemoglobin each week while on the control diet of salmon bread

plus canned salmon plus "Klim," a skim milk powder. Therefore, from the total hemoglobin removal each 4- or 5-week period we subtract 40 or 50 gm. to get the true *net effect* of the iron or liver, as the case may be. This dog's standard reaction to 300 gm. pig liver daily per 2-week feeding is 99 gm. hemoglobin. In Table 1 the effect of adding 40 mg. Fe to the basal ration daily for 2 weeks is 60 gm. hemoglobin and of feeding 400 mg. Fe daily for 2 weeks is 87 gm. hemoglobin production. The first dose of 40 mg. Fe daily we call the *optimum dose* because it seems to be the amount of Fe which added to the basal diet is utilized to the best advantage. Probably smaller doses would be utilized to equal advantage, but the return in hemoglobin is smaller and the chance of error in estimation because of physiologic variables is obviously larger. As the dose is rapidly increased the utilization falls off and 400 mg. Fe daily (10 times the optimum dose) gives less than twice the return in new hemoglobin.

TABLE 2.—IRON BY MOUTH. COMPARISON OF VARIOUS IRON SALTS.

Dog No.	Iron intake and hemoglobin output per 2 weeks' feeding.				Hemoglobin output per 2 wks. feeding liver, 300 gm. daily, gm.
	Type of iron salt.	Fe, daily dose, mg.	Hemoglobin output due to iron, gm.	Percentage of Fe appearing as hemoglobin.	
26–164 . . .	Ferrous sulphate	40	48	29.0	89
26–164 . . .	Ferrous sulphate	400	79	4.7	89
29–326 . . .	Reduced iron	40	33	20.0	69
29–326 . . .	Reduced iron	400	65	3.9	69
30–121 . . .	Reduced iron	40	49	29.0	87
30–121 . . .	Reduced iron	400	57	3.4	87
27–240 . . .	Iron cit. scales	40	54	32.0	97
30–115 . . .	Iron cit. scales	400	92	5.5	118
27–238 . . .	Fer. am. cit. green	40	46	28.0	
27–238 . . .	Fer. am. cit. green	400	75	4.5	

Much has been written about the availability of various iron salts, in the ferrous or ferric form, in the reduced state, as organic or inorganic salts, but in spite of all this work, sharp differences of opinion are to be found in the literature. Under the conditions of these experiments there appears to be no difference as to what soluble iron salt is used. Table 2 gives some typical experiments and the determining factor is the amount of the metal itself. Many other experiments with different iron salts have been done from time to time and some have been reported in earlier publications.[11] The experiments in Table 3 should be mentioned at this time, and with few exceptions the iron used in these experiments was in the form of ferric citrate scales.

One particular dog (29–326), in Table 2, should be reviewed, as it differs so conspicuously from the average. This dog is healthy

and has been continuously anemic under observation for 3 years and during all this time has been uniformly subnormal in its reaction to standard diets and iron therapy. On the average, from large numbers of experiments,[8] it is found that the anemic dog averages a net hemoglobin output of 95 to 100 gm. as the result of feeding 300 gm. pig liver daily for 2 weeks. Likewise approximately the same figure, an output of 90 to 95 gm. of hemoglobin, is observed in experiments in which Fe, 400 mg., daily is given for 2 weeks. Average figures for the optimum intake of iron—Fe, 40 mg., daily for 2 weeks—show an output of about 55 gm. hemoglobin. Although Dog 29-326, Table 2, is uniformly low in its hemoglobin output on standard diets, the ratios are as indicated in the average dog. Its hemoglobin output due to liver is 69 gm., the output due to iron (400 mg. daily) is 65 gm. hemoglobin, and the output due to the optimum dose of iron (40 mg. daily) is 33 gm. hemoglobin. Other dogs will show a consistent hemoglobin production much above normal—compare Dog 24-45, Table 3. We have some experiments to indicate that a dog raised on a favorable diet (liver) is apt to be permanently more active in subsequent hemoglobin regeneration than is the case in dogs raised on salmon bread and milk. We have no final comment relative to these individual physiologic peculiarities except to add that some dogs can run faster and further than others. To say that one dog has a physiologic mechanism that is more or less efficient in producing new hemoglobin, as compared with the average, gives little comfort to the investigator, but it is not an unfamiliar situation in physiology.

TABLE 3.—IRON BY MOUTH. SUMMATION DUE TO LIVER PLUS IRON AND LIVER CONTROL.

Dog No.	Iron intake and Hb. output per 2 wks.' feeding.			Hemoglobin output per 2 wks.' feeding.	
	Fe, daily dose, mg.	Hemoglobin output due to iron, gm.	Percentage of Fe appearing as Hb.	Hemoglobin output due to liver alone, 300 gm. daily.	Iron, 400 mg., plus liver, 300 gm., daily.
24-89	400	87	5.2		
27-238	40	49	26.0		
27-238	400	80	4.3		
27-238	450	74	3.5		
27-234	40	72	39.0	109	
27-234	400	...	...	...	125
27-234	400	117	7.0	93	129
30-115	40	49	26.0	118	
30-115	400	102	5.5	118	
24-45	40	95	57.0	121	
24-45	400	154	9.2	121	176
27-236	400	92	5.5	77	118

Dog. 30-115 splenectomized.

Table 3 gives more experimental data related to the feeding of iron by mouth. The *summation of iron and liver* is well shown in the latter half of Table 3. These dogs when given liver, 300 gm., and iron, 400 mg., daily for 2 weeks show an average production of 141 gm. hemoglobin. From iron, 400 mg., alone the average figure is 93 gm. hemoglobin. From liver, 300 gm., alone the average figure is 97 gm. hemoglobin. If we allow one-half of the liver production, or 48 gm. hemoglobin, plus 93 gm. hemoglobin from iron, we get the figure 141 for the summation which is much too perfect an agreement but at least supports the theory of summation due to organic and inorganic factors. This summation effect has been pointed out in an earlier paper.[6] It was found that whole liver ash contains about one-half the potency of whole liver, and in the face of maximum iron intake it seems unlikely that additional iron coming from the liver would have much if any added effect, so for the summation effect we calculate only one-half the total liver potency of 97 gm. hemoglobin.

It may be permissible to estimate the absorption of iron in Tables 2 and 3 from the output of hemoglobin in the several experiments. We may compute the amount of iron contained in the new-formed hemoglobin on the basis of 10 mg. Fe = 3 gm. hemoglobin and the fourth column in Table 3 shows the percentage of iron in the new hemoglobin related to the iron given by mouth, and we may call this the *percentage utilization of the iron.* For the 40-mg. Fe daily intake for a 2-week period, the average percentage appearing as new hemoglobin is 35%, and the average net hemoglobin production is 55 gm. For the larger dose of iron (400 mg. Fe) the average percentage utilization is 5.3% and the average net hemoglobin production is 91 gm. This, of course, is net hemoglobin production over and above the output due to the standard basal ration.

In spite of every effort to maintain uniform conditions in these dogs, we observe some variation in hemoglobin output in repeat experiments. We must attribute these changes in reaction to unknown physiologic variables, but the average values are reasonably constant and have some significance.

Table 4 shows the influence of salmon bread feeding alone upon hemoglobin regeneration. Practically all of these dogs have been carefully standardized on salmon bread diet for continuous periods of 10 to 15 weeks. Many of these dogs are unusually active in hemoglobin regeneration and are now more active than during earlier periods as reported in previous publications. The reasons for this cannot be detailed at this time but will be reviewed soon in another publication.

We may take the figures for hemoglobin regeneration and express them in terms of Fe, as shown in Column 5, Table 4. When we compare this figure with the iron contained in the food (salmon

bread) we see an average of 40% *utilization* of this food iron. It seems certain that other salts have a slight but definite effect upon hemoglobin regeneration and certainly protein fractions have a definite effect. It is impossible to state how effective this food iron is as compared with the optimum dose of Fe (Tables 2 and 3), which is given as 35% utilization. It is proper to inquire as to the percentage utilization of iron when given in the liver feeding. Liver as fed contains 18 mg. Fe per 100 gm. fresh tissue. The dog on 300 gm. liver daily for 2 weeks receives 756 mg. Fe. The average net hemoglobin output is 100 gm. which is equivalent to 335 mg. Fe, or a 44% utilization of iron. It is probable that the food iron utilization is not unlike the utilization of iron salts in optimum dosage as given in these experiments, but too many factors come in to make any dogmatic statement on this important point.

TABLE 4.—THEORETICAL UTILIZATION OF FE IN SALMON BREAD.

Dog No.	Amount of S. bread fed, gm.	Iron intake in bread per week, mg.	Hemoglobin output per week, gm.	Hemoglobin output as Fe per week, mg.	Ratio, Fe output in Hb. to intake in food, %
26–164	250	83	6	20	24
26–102	200	66	10	34	52
26–102	275	90	10	34	38
27–236	275	90	11	37	41
29–65	300	99	15	50	51
27–240	300	99	13	44	44
27–240	300	99	16	54	55
29–326	325	107	8	27	25
27–238	350	115	18	60	52
23–1	350	115	11	37	32
33–14	375	123	22	74	60
33–13	400	132	14	47	36
30–115	400	132	18	60	45
30–121	450	148	12	41	28
30–114	450	148	11	37	25
30–116	450	148	17	57	39
24–45	450	148	18	60	41

Salmon bread, 100 gm. as fed contains 4.68 mg. Fe.
Average ratio of Fe output as hemoglobin to Fe intake in salmon bread = 40%.
Dogs 29–65 and 30–115 are splenectomized.
Dog 26–164 has definite chronic nephritis.

Table 5 shows a satisfactory experiment in which a large amount of colloidal iron is given intravenously during a 2 weeks' period—50 mg. per day, or 700 mg. per 2 weeks, or expressed as hemoglobin on a quantitative basis, 210 gm. We note that the total hemoglobin removed during 18 weeks is 504 gm., and allowing a base line output of 15 gm. per week, or 270 gm. hemoglobin, for the 18 weeks, we observe a net production of 234 gm. hemoglobin as compared with the theoretical of 210 gm. hemoglobin. If we use a basal output of 16 gm. hemoglobin, the figures for actual and theoretical hemo-

globin return are almost identical. We may say that within the uncontrollable physiologic variations this experiment shows a quantitative return or regeneration of hemoglobin due to Fe given intravenously.

TABLE 5.—COLLOIDAL IRON INTRAVENOUSLY. QUANTITATIVE HEMOGLOBIN OUTPUT DURING 8 WEEKS.

Dog 30–117.

Diet periods, 1 week each. Food, grams per day.	Food cons., %.	Wt., kg.	Plasma, vol., cc.	R.B.C., mil.	Blood, Hb. level, %.	Hemoglobin remov. bled, gm.
Bread, 450; salm., 100; Kl., 40	100	15.4	945	4.5	48	1.3
Fe, 50 mg.; br., 450; salm., 100; Kl., 40	100	15.3	814	7.1	94	49.4
Fe, 50 mg.; br., 450; salm., 100; Kl., 40	100	15.0	854	7.7	87	71.2
Bread, 450; salm., 100; Kl., 40	100	14.8	846	6.5	67	61.6
Bread, 475; salm., 100; Kl., 40	100	14.7	891	5.1	70	27.0
Bread, 475; salm., 100; Kl., 40	100	14.9	903	5.3	59	49.2
Bread, 475; salm., 100; Kl., 40	100	15.1	958	4.9	51	24.4
Bread, 475; salm., 100; Kl., 40	100	15.1	956	4.7	64	38.5
Bread, 475; salm., 100; Kl., 40	100	15.0	952	...	79	36.6
Bread, 475; salm., 100; Kl., 40	100	15.1	944	4 5	48	1.1
Bread, 475; salm., 100; Kl., 40	100	15.4	994	4.9	63	25.1
Bread, 475; salm., 100; Kl., 40	100	15.6	957	5.0	57	22.3
Bread, 475; salm., 100; Kl., 40	100	15.4	974	5.1	50	23.4
Bread, 475; salm., 75; Kl., 40	100	15.8	1017	5.2	44	19.2
Bread, 475; salm., 75; Kl., 40	100	15.8	1033	4.5	45	10.1
Bread, 475; salm., 75; Kl., 40	100	15.7	994	4.7	46	1.2
Bread, 475; salm., 75; Kl., 40	100	15.0	952	5.2	53	24.0
Bread, 475; salm., 75; Kl., 40	100	15.1	959	5.1	47	18.4
Bread, 475; salm., 75; Kl., 40	100	15.3	968	4.8	45	1.2
					Total	503.7

Total Fe = 700 mg. = 210 gm. Hb.
Basal output = 15 gm. Hb. per week; 18 weeks = 270 gm. Hb.
Theoretical return 210 + basal output 270 = 480 gm.

If we examine Table 5 in more detail, we see that even the very active bleeding during the period of Fe injection does not keep the anemia level down to the base line, and it requires a 6 weeks' after-period to reduce the surplus "carry over" related to the Fe stored in the body and utilized in this emergency. The protein building stones needed for the *globin* part of the hemoglobin must come from the salmon bread or from body stores. It is significant that the combination of this same dose of intravenous Fe plus 300 gm. liver fed daily for the same 2 weeks does not cause any increase in the total hemoglobin output (Table 6, Dog 30–117). It would seem that this reaction is about the top limit for hemoglobin production in these standardized dogs beyond which no added factors have influence. It is not unreasonable to suppose that the hemopoietic apparatus of the dog has a limit to its productive capacity, and under these conditions that limit is presumably reached.

TABLE 6.—IRON BY VEIN AND ALMOST QUANTITATIVE HEMOGLOBIN OUTPUT.

Dog No.	Iron, daily dose, mg.	Hemoglobin output, gm.	Theoretical hemoglobin return from Fe by vein, gm.	Ratio of actual Hb output to theoretical Hb. output, %	Control hemoglobin output.	
					Iron, 40 mg. daily, oral.	Liver, 300 gm. daily.
30-114	8	47	33	142	...	99
27-238	17	59	71	83	63	
27-238	20	104	84	124	49	
27-234	20	81	84	97	...	109
27-239	20	95	84	113	...	90
24-89	21	98	88	111	56	
27-238	29	94	121	78	63	
27-236	32	167	134	125	...	77
30-117	32	137	134	100	...	99
27-238*	32	151	134	113	49	
30-117	50	238	209	114	...	99
30-117†	50	195	209	93	...	99

* Dog. 27-238—Fe, 400 mg., daily by mouth in addition to intravenous Fe.
† Dog 30-117—Liver, 300 gm., daily by mouth in addition to intravenous Fe.

Table 6 shows a number of satisfactory experiments with colloidal iron given intravenously. Moreover, some of the experiments show such large doses of Fe that the "carry over" effect lasts 6 weeks beyond the period of intravenous Fe injection (compare Table 5). Obviously all the iron is carefully saved and eventually appears as new hemoglobin. The tremendous amount of protein building material needed to form the required globin is produced without apparent difficulty and comes either from the salmon bread or body stores. It appears that about 70 gm. hemoglobin per week, or 10 gm. a day, is about the absolute maximum hemoglobin production for these dogs under these conditions. When we recall that about 10 gm. hemoglobin per week is a high average for these dogs on the basal salmon bread diet, this peak production of 10 gm. hemoglobin per day should excite our admiration for the flexible machine which we call the hemopoietic system.

Actual hemoglobin output, compared with theoretical hemoglobin output based on the iron given intravenously, is an interesting figure (see Column 5, Table 6). This average percentage is 105, with maxima and minima of 125 and 78%. This should seem to indicate that these anemic dogs conserve all the Fe given intravenously, and within a period of 6 to 8 weeks return every last bit of it as new-formed hemoglobin. In figuring this average for Table 6 we did not include the first figure (Dog 30-114), where a small dose of iron gave an apparent return of 142% which might indicate some physiologic stimulus; when the amount of iron administered is quite small the physiologic variables may introduce large errors and it did not seem wise to include this in an average.

TABLE 7.—IRON BY VEIN AND THE INFLUENCE OF SPLENECTOMY AND THE ECK FISTULA.

Dog No.	Iron, daily dose, mg.	Hemoglobin output, gm.	Theoretical hemoglobin return from Fe by vein, gm.	Ratio of actual Hb. output to theoretical Hb. output, %.	Control. Liver, 300 gm. daily.	Remarks.
29–65 . .	50	101	209	48	99	Splenectomy.
30–115 . .	50	126	209	60	118	Splenectomy.
30–61 . .	50	120	209	52	82	Eck fistula.
26–124 . .	50	112	209	54	88	Eck + splenectomy.

Table 7 shows that large doses of iron given intravenously are not conserved as effectively by the splenectomized or the Eck fistula dogs as by the normal animal. That splenectomy lessens the capacity of the dog to conserve intravenous iron is perhaps not surprising, as we eliminate a considerable portion of the cells which make up the reticulo-endothelial system. As the colloidal iron is not completely taken up, we must assume that it is lost to the body probably by way of the intestine.

It is more difficult to explain why the Eck fistula does not utilize efficiently the iron given intravenously. Combining the Eck with a splenectomy apparently does not further decrease the utilization of intravenous iron. In the Eck fistula the portal blood is shunted direct into the vena cava so that it does not flow through the liver. The blood flow through the liver is about one-third normal and only by way of the hepatic artery, so that the Kupffer cells cannot be active as usual in the removal of material like colloidal iron. On the other hand, the Eck fistula liver is smaller than normal and functionally inefficient in many ways so that one may choose to explain the lowered hemoglobin output on this basis. Further work touching this point will soon be published.

Discussion. Our thesis relative to iron utilization in anemia in the healthy dog reads about as follows: Iron given intravenously to a normal anemic dog will be eagerly utilized to form new hemoglobin practically on a quantitative basis, 10 mg. Fe = 3 gm. hemoglobin. Therefore, in the same dog under certain conditions we may estimate the amount of absorbed iron (coming from the intestine) from the amount of new-formed hemoglobin. It may be argued that iron given intravenously is different from iron coming into the portal vein from the intestine, but the weight of evidence favors the belief that in this emergency, due to anemia, the healthy dog will utilize quantitatively the Fe as it comes into the circulation just as under similar circumstances it utilizes quantitatively[10] hemoglobin given intravenously to rebuild new hemoglobin for red cells.

Assuming that under these conditions new-formed hemoglobin is

a reasonably accurate measure of Fe absorbed from the intestine, we may calculate the ratio of Fe ingestion to new hemoglobin production. For the optimum dose of iron (40 mg. daily) this ratio will be about 3 to 1, or a 35% utilization of ingested iron. For larger doses of iron (400 mg. daily) this ratio will be about 20 to 1, or a 5.3% utilization of the iron given by mouth. This is to be compared with the 10 to 1 ratio for the feeding of whole blood cells by mouth—for 10 gm. of hemoglobin fed there is a return of only 1 gm. of new hemoglobin in the standard dog.[10]

Standard salmon bread feeding is of considerable interest (Table 4) and we may compare the hemoglobin output with the intake of food iron contained in the bread. The figures show that the salmon bread iron gives a 40% utilization of this iron.

When we consider liver feeding the problem becomes more complex and there is no parallelism between iron content of liver and its potency for new hemoglobin production. Liver ash may account for nearly one-half the potency of whole liver, but other salts besides iron are concerned and certainly protein complexes or intermediates are important. On the average, liver feedings show that the dog utilizes about 44% of the Fe contained in normal pig liver in the production of the new-formed hemoglobin.

If one is driven to a generalization it would be that moderate doses of soluble iron salts or food iron contained in salmon bread or pig liver are utilized to about the same degree by the healthy anemic dog, that is, a 35 to 45% utilization. One must admit that there are many organic and inorganic factors as well as iron which influence hemoglobin production in anemia and any dogmatic generalizations about "food iron" are not safe. One finds many strong statements about "food iron" in the literature, and perhaps these writers are to be commended for their courage. Those who believe that "food iron" and its absorption are relatively simple questions are perhaps happy in that state of mind, but the structure of their argument is a frail refuge against the storms of adversity.

Furthermore we have observations to show that infection and intoxication will modify internal metabolism and limit the output of hemoglobin in anemia. Bile secretion will also modify the production of hemoglobin in this type of anemia and these experiments are soon to be published. Table 6 shows that the Eck fistula and splenectomy may modify reactions to Fe given by vein.

Flexibility is a word which applies to the internal pigment metabolism of the anemic dog, and it must always excite our admiration even if it is the despair of students in this field. The standardized anemic dog has a uniform output of hemoglobin per week, while on a standard ration of salmon bread—also a uniform reaction to the administration of iron salts and there is about a 35 to 40% utilization of the contained iron whether inorganic or food iron. When iron

is given intravenously we observe a quantitative return, even when enormous doses are given, and the body finds the needed building material to supply the *globin*—a protein making up about 95% of the hemoglobin molecule. When an anemic dog is fasted and given iron intravenously the dog will form large amounts of hemoglobin, and much of it must come from body protein stores. It has been shown in this laboratory[2] that a considerable part of this new hemoglobin is formed by conservation of material which under control fasting conditions would be wasted as urea in the urine. Again, we may give amino acids or organ fractions almost free of iron and cause increased hemoglobin production by the anemic dog. Now the dog must draw Fe from depleted stores or utilize the food iron even more completely. We have found it possible to reach the end of the iron stored in the body and observe a fall in hemoglobin production under such conditions (Table 24, accompanying paper) but the iron conservation within the body must be truly remarkable.

Summary. Iron given intravenously to these standard anemic dogs, in large or small doses, will be returned quantitatively as new-formed hemoglobin on the basis of 10 mg. Fe = 3 gm. hemoglobin (Table 6).

When iron is given by mouth to these standard anemic dogs the influence on hemoglobin production is not proportional to the amount of iron administered. An optimum dose of iron (40 mg. Fe per day for 2 weeks, or 560 mg.) will give a net output of about 55 gm. hemoglobin, and this means about a 35% utilization of the iron given. With larger doses the hemoglobin output increases a little, and with 400 mg. Fe daily the net output would average about 95 gm. hemoglobin, or about a 5% utilization of the iron given by mouth.

Iron contained in salmon bread under certain conditions may be utilized by these anemic dogs up to about 40% to produce hemoglobin. Iron in the normal liver when fed may show a 45% utilization of this tissue iron.

When liver feeding is combined with iron feeding, there is a definite summation effect (Table 3).

When intravenous iron in large doses is combined with liver feeding or iron by mouth, there is no evidence of summation (Table 6). This probably means that the top functional capacity of the body to produce hemoglobin has been reached—about 10 gm. hemoglobin output per day.

Iron salts are utilized with equal facility by the dog to produce hemoglobin when given by mouth in the ferrous, ferric or reduced state. The determining factor is the amount of the iron metal.

The Eck fistula and splenectomy lessen the capacity of the anemic dog to conserve and utilize iron given by vein to produce new hemoglobin (Table 7).

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II. IRON METABOLISM.

Its Absorption, Storage and Utilization in Experimental Anemia.

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The most significant point to be made in this paper is the *rapid turnover of iron* coming in from the intestines in these standard anemic dogs. It may be accepted without debate that the liver is the main storehouse for iron in the normal dog, for although the spleen may contain as much or more per gram tissue weight, the liver mass is about 10 times that of the spleen. Furthermore, the liver is a storehouse for materials which may be used in various anemic states to further the construction of new red cells and hemoglobin. What more logical hypothesis can be argued than

that the liver is active in producing intermediates which go into the manufacture of the large hemoglobin molecule? How much of this assembly of intermediates might go on in the liver or bone marrow would be a matter of debate.

With this reasonable hypothesis we expected confidently that in bloodfree organs depleted of iron stores by anemia, it would be possible to demonstrate some store of iron following a single dose of iron citrate by mouth. With the large doses given, one could assume with confidence the absorption of not less than 20 mg. Fe per dose which should be readily demonstrable in the liver if it is detained there during the elaboration of intermediates. No such temporary storage can be demonstrated (Tables 1 and 2). With repeated doses of Fe by mouth some liver storage of iron can be demonstrated but it is always small and represents usually an insignificant amount of the intake. It would be rash to say that this iron has no contact with the liver, but its contact must be fleeting and it seems probable that in the anemic dog under favorable conditions the badly needed iron is turned over in the internal metabolism with speed and dispatch, appearing at its ultimate destination as finished hemoglobin in the short interval of 24 to 48 hours.

The *red bone marrow* as viewed by the physiologist has a most unfortunate makeup and location. It is scattered all through the bone skeleton, and iron analyses are complicated by this abundance of bone with its calcium and phosphorus. Its mass in these dogs[7] amounts to about two-thirds the weight of the liver and it is most difficult of perfusion. Large errors must come in as we attempt to estimate the amount of iron in the marrow and even more when we would differentiate between hemoglobin iron and parenchyma iron. Before this matter is settled we must perfect our methods of assay and measurement. When we are trailing an elusive element like iron we may liken the red marrow to a jungle in which this metal may promptly take refuge from the hunter and even change its form (into hemoglobin) to avoid detection.

Methods. Adult dogs in good physical condition were used in all of these experiments. The animals were made anemic by blood withdrawal using a hypodermic needle and were then maintained at a hemoglobin level of $\frac{1}{2}$ to $\frac{1}{3}$ normal for at least 2 months to exhaust completely the iron reserves. During this time frequent blood samples were taken and red cell percentages and hemoglobin content were followed. The acid-hematin method[13] was used in the latter determination, 100% hemoglobin being taken as 13.8 gm. per 100 ml. blood. Plasma and blood volume determinations by the Brilliant Vital Red dye method[9] were made at intervals of about a week. Unless otherwise specified, the animals were finally placed on a diet of low iron content for at least 1 week prior to the testing of the material, in order to eliminate the effect of iron which might have been taken in with the kennel ration of hospital table scraps on which they were maintained during the initial period. This low iron diet consisted of white bakers' bread, canned salmon, "Klim" (a skimmed milk powder), and

water; the amounts of each constituent being varied somewhat to meet the individual needs of the dogs. The daily iron intake on this diet was about 5 mg. When such a diet was employed for periods of more than 2 weeks, cod-liver oil and a salt mixture (McCollum and Simmonds without iron) was added to it in order to prevent the onset of deficiency disease.

The dogs were subjected to perfusion approximately 24 hours after the last administration of the material to be studied. This perfusion is described in detail by Whipple[16] elsewhere. Briefly, it involves infusion, under ether anesthesia, of a warm glucose-Locke's solution in a cannulated jugular vein while blood is removed simultaneously at an equal rate from a cannula in one of the carotid vessels. As the heart begins to fail, adrenalin is injected with the infusing solution. When the heart stops, perfusion is discontinued. The viscera are promptly removed, sections are taken for histologic examination, and after rinsing in Locke's solution they are wrapped in towels soaked in the solution and placed in the refrigerator for 3 to 4 hours.

In some cases samples of muscle were analyzed for muscle hemoglobin. For this procedure samples were used as soon after the autopsy as possible. The method,[16] in short, consists in mincing 10 gm. of fresh striated muscle. Enough 0.4% NH_4OH is added to make a total volume of 50 ml., and with occasional shaking the mixture is allowed to stand about 16 to 20 hours in the refrigerator to extract the pigment. It is then filtered through gauze and the filtrate is then further filtered through a medium filter paper. The final solution should be quite clear. A 10 ml. aliquot portion is treated with 4 drops of concentrated HCl, heated to 56° C. in a water bath for ½ hour, cooled, and filtered. The solution is then compared with an acid hematin standard in a colorimeter.

*Preparation for Analysis.** Tissues are ashed by a wet ashing procedure. Samples of from 10 to 70 gm. are weighed and transferred to 800 ml. Kjeldahl flasks. Two or three samples of each organ are employed. They are then allowed to autolyze at room temperature for 24 to 48 hours. Forty milliliters of fuming HNO_3 are added and they are allowed to stand about 24 hours. A few glass beads and 20 ml. of concentrated sulphuric acid are introduced to the flask and the contents are digested over a moderate flame until charring first becomes apparent. From this point perchloric acid (60%) is added 2 ml. at a time at frequent intervals with continued boiling. If there is danger of the material becoming dry at any time, sulphuric acid is added. Digestion is continued until the solution is clear and colorless, or a pale yellow turning to colorless on cooling. Boiling is continued another 20 minutes, the solution is cooled, 20 ml. of water added and heating resumed until the water is driven off. This last step may well be repeated. After it has cooled the solution is transferred to a 100 or 200 ml. volumetric flask by means of water distilled from glass. The

* Unless specific precautions are taken to prevent it, dry ashing is claimed by some to yield pyrophosphates which definitely interfere with the determination of iron by colorimetric methods. Pyrophosphates are said not to be produced by wet ashing (McFarlane, Biochem. J., 26, 1022, 1034, 1932).

The color developed by CNS^- is greatly affected by the pH of the solution. Dry ashing with modifications may be preferred by many using the thiocyanate procedure as the acid concentration of the final material may be controlled, this being difficult with the wet ashing method. In the use of the "iodo-quinoline" reagent we feel we have control of the pH of the final solution as a result of the precipitation and subsequent buffering of the digestion mixture.

In using the potentiometric titration with titanous sulphate difficulties are encountered to be sure, but it was never felt that these were traceable to the wet ashing procedure.

Large quantities of tissues must be dealt with when the tissues are depleted of iron and it was further felt that dry ashing would be applied to such amounts only with difficulty.

volume is readjusted after cooling and the final solution is stored in convenient bottles.

Aliquot samples are then analyzed for iron by either the electrometric titration with titanous sulphate, or colorimetrically by means of iodo-quinolin reagent. As a rule, from 1 to 6 aliquots of each digestion sample were analyzed by both methods.

*Potentiometric Titration with Titanous Sulphate.** Aliquots of tissue digests and standards (standard solution made by dissolving standard iron wire in dilute H_2SO_4; 20 ml. of dilute solution equivalent to 1 mg. Fe) are carefully pipetted into 125 ml. Florence flasks and 7 ml. of concentrated sulphuric acid added. The contents are then brought to a boil over an open flame, and with constant rotation are kept at the boiling point for at least 2 minutes following the appearance of dense white fumes. Care must be exercised that the volume does not fall below about 5 ml. After cooling about 25 ml. of 20% H_2SO_4 (O_2-free, stored under N_2) are added; they are covered with small watch glasses and placed on the steam bath overnight.

Titration with dilute titanous sulphate solution (about 3 ml. equivalent to 0.05 mg. iron) against a potentiometric indicator is then carried out under an atmosphere of CO_2, the flasks containing the samples being immersed in a water bath at 90 to 100° C. and constantly shaken by means of a motor through an eccentric lever. The titanous solution is stored under an atmosphere of N_2 and is supplied to the burette much as originally described by King and Washburne.[10] Daily standardization of this solution is essential.

When used for the determination of such small amounts of iron as was occasionally necessitated, this method was not as satisfactory as might be wished. However, it gave better results in the writer's hands than did the colorimetric thiocyanate or thioglycollic methods, and seems to be the best method for analysis of materials high in Ca and P, in conjunction with wet ashing.

Iodo-quinolin ("Ferron") Colorimetric Method. This procedure was suggested by the comparator method of Yoe.[19] It has been adapted to the use of the colorimeter but such use demands that the standard and unknown samples be nearly equivalent in iron content since the color developed does not have the same quality at widely different concentrations. This necessitates a preliminary trial determination to find the proper aliquot of the sample digest to be used. The color developed is quite stable as contrasted with the thiocyanate and thioglycollic iron salts, and the reaction is very sensitive.

Aliquots of the tissue digests such as will contain about 0.1 mg. of iron, and corresponding standards are pipetted into 100 ml. centrifuge tubes. A drop of 30% H_2O_2 is added with shaking and a drop of phenolphthalein indicator solution introduced; 40% NaOH is added drop by drop with shaking until the solution is decidedly alkalin, and the sides of the tube are washed down. Thorough mixing is essential at this point to avoid stratification later. The solutions are then allowed to stand overnight. After stoppering with corks and balancing in hangars, the solutions are centrifuged at about 2500 r.p.m. for 35 minutes. Six unknowns and duplicate standards are easily accommodated in this way. Following removal from the centrifuge (without excessive jarring) the supernatant liquid is poured off and discarded. Two milliliters of 0.666 *N* HCl are added to dissolve the ferric hydroxid precipitate and the sides of the tube are washed with 10 ml. of water. A little vaselin is applied to the tips of the tubes and the supernatant liquid is decanted into 25 ml. volumetric

* The writers are deeply indebted to Dr. S. H. Bassett of the Department of Medicine for many invaluable suggestions regarding this method.

flasks. The sides of the tubes are washed with 5 ml. of M/5 potassium acid phthallate, and this added to the flask. This last washing is repeated with another 5 ml. of solution.* After shaking, 1 ml. of a 0.2% aqueous solution of 7-iodo-8-hydroxy-quinolin-5-sulphonic acid is added and the solution made up to volume with water. The colors are then matched in a colorimeter. It was found that a Corning "Signal Red" filter was of assistance in making the readings. With the standard solution set at 15 mm. the unknown should read between about 14 and 16 mm., otherwise the correct aliquot should be calculated and the determination repeated.

This method checked well with the electrometric procedure and was much more dependable, in general. The electrometric procedure, however, is highly preferable for samples containing large amounts of Ca and P.

Experimental Observations. We wish to point out the importance of *blood-free organs* in this type of experiment. The tables below show very small changes in iron content of the viscera and the presence of small amounts of red cells and hemoglobin would obscure completely any such changes. A successful experiment with viviperfusion reduces the red cell hematocrit to less than 1%, or about 1 to 2% of the normal red cell hematocrit in the dog (50%). These figures given for the terminal sample at the end of the perfusion are actually too high, as the packed red cells are mixed with a variable amount of calcium oxalate which increases the bulk of the material read as packed red cells. The blood at the end of the perfusion is a delicate pink and the blood does not clot so that the organs, removed promptly and placed in a moist cloth, will drain practically free of this greatly diluted blood. The lungs are usually snow white, or a delicate pale gray if the dog has inhaled coal dust or dirt during its life. The spleen presents a pale red color but the liver is a pale buff color. The pancreas is white and the intestines a very pale brown color. The kidneys are a pale brown color in the cortex with almost white pyramids. The rib marrow presents a pale red color. The muscles present the normal color due to the presence of the muscle hemoglobin.

We may ask concerning the error due to contained blood if the tissues and organs are not perfused in this way. The normal dog with a red cell hematocrit of 50% shows about 20 gm. hemoglobin per 100 cc. blood or 67 mg. Fe per 100 cc. whole blood or 50 cc. packed red cells. That is, 1 cc. packed red cells contain more than 1 mg. Fe. After this viviperfusion, 100 cc. whole blood contains about 1 mg. Fe and the blood does not clot and will drain off well. The error introduced by this dilute blood after perfusion must be very small and actually within the method accuracy for iron analysis.

Gravity perfusion of viscera after death has been used by some workers but it is quite unsatisfactory and introduces large errors.

* The use of HCl-potassium acid phthallate buffer to provide a solution pH of about 2.6, near which the color development is a maximum, was suggested by Dr. Yoe in a personal communication to P. F. H. He also proposes the name "Ferron" for the 7-iodo-8-hydroxy-quinolin-5-sulphonic acid reagent.

The red blood cells cannot be washed out with anything like completeness and edema develops promptly. By the viviperfusion method edema may develop toward the end, but it is slight and does not introduce significant errors. The pancreas is usually first to show this edema.

The *spleen and marrow* are exceptions, and even with perfect technique of viviperfusion these tissues contain some red cells within the sinusoids where the circulation is so inactive. From extractions and analyses of spleen the contained hemoglobin will account for about one-third of the iron found by analysis, and it is probable that the red marrow contains something like the same amount of hemoglobin after viviperfusion.

Histologic sections were studied in all these cases and give some help. After perfusion the spleen contains more mature red cells than does the bone marrow, and the red cells are found both in the vascular spaces and interstitial spaces. The picture in the spleen is pretty constant histologically. The perfused marrow shows more variety in its area and general makeup, but on the average appears to contain fewer mature red cells than the spleen. Nucleated red cells of various types are numerous but their contained hemoglobin is much less, of course, than in the mature cells. The red marrow therefore probably contains proportionately less hemoglobin iron than the spleen because the marrow shows a higher total iron than any other tissue per gram weight in the anemic dog. More study must be given to these points.

TABLE 1.—IRON CONTENT OF BLOOD-FREE TISSUES OF ANEMIC DOGS. RAPID TURNOVER OF IRON.

Dog No.	Anemia.		Iron intake.		Mg. Fe per 100 gm. fresh tissue.							
	Hb. level (%).	Duration (weeks).	Daily.	Duration (days).	Liver.	Spleen.	Ribs.	Kidneys.	Pancreas.	Heart.	Psoas.	Lungs.
32-44	50-60	12	400 mg. Fe orally	1	1.4	8.6	5.1	2.6	2.4	2.5	4.5	3.7
32-374	50-60	12	1000 mg. Fe orally	2	1.9	8.7	5.3	2.2	1.1	2.3	2.7	5.8
33-190	40-50	8	400 mg. Fe orally	7	5.0	11.2	7.2	2.1	1.6	3.6	3.5	2.8
27-235	40-60	250	400 mg. Fe orally	5	17.8	10.4	...	2.1	1.1	2.9	3.0	2.3
33-85	40-60	24	Limited diet (Table 4)	..	1.7	7.9	...	1.2	0.7*	2.6	3.1	5.2
33-325	40-55	9	Liver	..	1.3	9.4	...	1.7	...	3.3	3.3	2.9
33-92	40-55	12	53 mg. Fe. intraven.	2	18.1	49.8	4.9	2.1	1.8	2.5	3.9	2.7
33-1	50-60	11	108 mg. Fe intraven.	2	26.8	75.2	4.7	2.2	1.2	2.1	3.3	3.1

* Edema.

Lungs contain a little more parenchyma iron than liver, kidney and pancreas—an average of not less than 3 mg. Fe per cent. These lungs are especially completely perfused as the capillaries are larger and the histologic sections show complete absence of red cells. There are no organic pigment deposits and intravenous iron does not cause any increase of this lung parenchyma iron. There are

some dust deposits in lungs and this material may contain some iron. Some substances related to oxygen transfer may be responsible for this excess iron. Two dogs (32–374 and 33–85, Table 1) show iron figures above normal, but nothing unusual was made out by histologic study to account for this excess.

Table 1 gives the iron content of various perfused tissues of anemic dogs on definite diets with a known intake of iron by mouth. Table 3 should be compared with Table 1 to give an essential base line. The various experiments listed in Table 1 are described in sufficient detail in the clinical histories of the various dogs which follow Table 1.

Clinical Histories. *Dog 32–44*, a fat, moderately active female mongrel terrier, weighing 19 kilos (Tables 1 and 2), had been maintained by suitable bleeding at a hemoglobin level of 50 to 60% (100% = 13.8 gm. hemoglobin per 100 ml. blood) for a period of 3 months. During this period the diet consisted of hospital table scraps. There followed a week's feeding of a white bread diet low in iron (see Methods). With the last day's ration there was incorporated 400 mg. of iron in the form of ferric citrate. After 22 hours the animal was perfused as described above. The final red cell hematocrit at the end of the perfusion read 0.4%. On analysis there was no evidence of iron having been stored in any of the tissues examined, even though this amount of iron by mouth in the anemic dog would result in the eventual production of 6 to 7 gm. hemoglobin. The iron content of the various tissues may be looked upon as being within the limits of control base line values (Table 2).

Dog 32–374, a large, inactive, lean male mongrel hound, weighing 20 kilos (Tables 1 and 2), had been maintained by suitable bleeding at a hemoglobin level of 60 to 80% for 2 months, followed by a period of 3 months at a level of 50 to 60% hemoglobin. During this whole time the diet had consisted of the regular kennel ration of hospital table scraps. The usual white bread diet low in iron was fed for 1 week and was supplemented during an additional 2 days with 1 gm. of iron per day, given as ferric citrate. As before the animal was perfused 24 hours following the last feeding. The final red cell hematocrit at end of perfusion read 0.4%.

TABLE 2.—WEIGHTS OF ORGANS OF PERFUSED ANEMIC DOGS AND TOTAL IRON CONTENTS.

Dog No.	Liver.		Spleen.		Kidneys.		Heart.		Pancreas.		Lungs.		Body wt., kilos.
	Wt., gm.	Iron, mg.	Wt., gm.	Iron, mg.	Wt., gm.	Iron, mg.	Wt., gm.	Iron, mg.	Wt., gm.	Iron, mg.	Wt., gm.	Iron, mg.	
32–44	450	6.3	51	4.4	72	1.9	136	3.4	37	0.9	121	4.5	19
32–374	523	10.0	47	4.1	70	1.5	227	5.2	61	0.7	150	8.7	20
33–190	260	13.0	47	5.3	60	1.3	110	4.0	25	0.4	90	2.5	11
27–235	455	81.0	57	5.9	109	2.3	133	3.9	38	0.4	111	2.5	14
33–85	425	7.2	40	3.2	100	1.2	176	4.6	107*	0.7	135	7.0	15
33–325	215	2.8	18	1.7	50	0.9	104	3.4	28	...	72	2.1	10
33–92	325	58.8	55	27.4	67	1.4	106	2.7	36	0.6	102	2.7	12
33–1	390	104.5	40	30.0	80	1.8	106	2.2	35	0.4	95	2.9	13

* Edema.

This amount of iron fed to an anemic dog (32–374) could cause the production eventually of not less than 13 gm. new hemoglobin, the equivalent of 44 mg. Fe which presumably would have been absorbed. Forty-four milligrams Fe should be readily recognized in these bloodfree organs if it is stored. We see (Table 2) that the liver contains 10 mg. Fe, a little more than the average base line. The spleen contains 4.1 mg. Fe, but if we deduct one-third for contained red cells we have but 2.8 mg. Fe for parenchyma iron. The bone marrow iron, of course, must be estimated with possible errors of some magnitude. We may say that one-third of the rib is red marrow and very little iron is found in true bone which triples the value of the iron contained in rib marrow, as the figures given are for the whole rib. The marrow volume[7] will be about two-thirds that of the liver and we should allow about one-third for Fe contained in red cells within marrow sinusoids. This dog (32–374) therefore would have about 38 mg. parenchyma Fe in its total red marrow—or a total of 51 mg. Fe in liver, spleen and marrow. The 44 mg. Fe presumably absorbed should be readily detected but this is contrary to fact. It would seem that either this iron is held in body fluids including plasma and corpuscles, or that there is a very rapid turnover of iron in this emergency with the iron reaching its ultimate goal in the hemoglobin of the red cell very promptly.

Dog 33–190, an extremely active female Boston bull terrier, weighing 11 kilos (Tables 1 and 2), following an anemia period of 2 months' duration at a level of 35 to 50% hemoglobin was placed for 1 week on the white bread diet low in iron. After this bread week, 400 mg. of iron per day were added to the diet in the form of ferric citrate, this supplement being continued for 7 days. During this last week the dog was not bled except for sampling, which was quite frequent in order to determine the time of appearance of new hemoglobin in the blood stream.

The dog was perfused 48 hours after the last feeding. The final red cell hematocrit after perfusion read 0.9%. The blood picture and hemoglobin production of the dog at various intervals during the 2 weeks may best be seen in tabular form.

Dog 33–190.	Hb. level (%).	Plasma vol (ml.).	Blood vol. (ml.).	Circulating Hb. (gm.).
At start of iron feeding	39	745	910	49
At end of iron feeding (perfusion)	62	725	1,045	89
Increase in circulating Hb.				40
Hb. removed in sampling				6.5
Hb. produced due to basal diet				6±
Total net Hb. production due to iron feeding				40

In Dog 33–190 the amount of hemoglobin produced on the white bread diet poor in iron is not known but is given as an average figure—6± gm. hemoglobin per week. The accompanying paper shows that the anemic dog fed 400 mg. Fe daily will put out about 45 gm. hemoglobin per week. This dog increased his store of circulating hemoglobin above the output due to the basal diet by about

40 gm. hemoglobin and has in reserve in his liver, spleen and marrow about 20 mg. Fe above the control values for these blood-free tissues. This amount of reserve iron could account for 6 gm. hemoglobin.

In Dog 33–190 (Tables 1 and 2) it is obvious that there is a very rapid turnover of the iron coming in with the food, and evidence of a little surplus storage of iron in the liver (9 mg.), spleen (1.3 mg.) and marrow (8± mg.). We emphasize again that the figures for red marrow are only approximations which are given for what they are worth. How many of the immature red cells may be washed out of the red marrow by the viviperfusion method used we cannot say, nor can we estimate with any accuracy the parenchyma iron held in marrow cells or tissues.

The parenchyma iron (Dog. 33–190) for other viscera and striated muscle fall within normal control limits. The heart muscle[16] is a little higher than normal and may be accounted for by the unusual activity of this dog.

Dog 27–235, a rather inactive adult female mongrel bull terrior, weighing 14 kilos (Tables 1 and 2), had been in the anemia colony of this laboratory for 7 years and had been maintained at an anemia level of 40 to 60% hemoglobin for the past 5 years. The dog was placed on the white bread low iron diet for a period of 8 weeks, followed by a fasting period of 2 weeks to assist in depleting the iron stores. The diet was resumed for 1 week, was supplemented for 5 days with 400 mg. of iron as ferric citrate each day, and 18 hours later the animal was perfused. The final red cell hematocrit after perfusion was less than 2.9%. The blood picture during the last few weeks of the experiment follows:

Dog. 27–235.	Hb. level (%).	Plasma vol. (ml.).	Blood vol. (ml.).	Circulating Hb. (gm.).
At beginning of fast	46	640	840	
At end of fast	50	620	815	
At start of iron feeding	41	785	1,000	56
At end of iron feeding	70	630	905	88
Increase in circulating Hb.				32
Hb. due to basal diet				5.4
Total net Hb. production due to iron feeding				26.6

Dog 27–235 shows a net hemoglobin output of 26.6 gm. hemoglobin, which may be related to the large doses of iron given in the 5 days before the perfusion. This same dog had been carefully standardized during its stay in the anemia colony. It was rated as above average in its capacity to form new hemoglobin on various diets. With 40 mg. Fe given during 2 weeks its hemoglobin output was 44 gm. hemoglobin, and with 300 gm. liver given daily for 2 weeks its output was quite high—127 gm. hemoglobin as compared with the average value of 95 to 100 gm. hemoglobin.

Dog 27–235 shows a net hemoglobin production of 26.6 gm. and contains some excess storage of iron in liver and spleen which would represent more potential hemoglobin production. The

spleen and liver together (Table 2) contain about 74 mg. Fe above the control level and we may say this is equivalent to 22 gm. hemoglobin. If we add this to the 26.6 gm. hemoglobin production we have about 49 gm. hemoglobin produced and in reserve, which we can state is due to the feeding of 2000 mg. Fe during the 5 days recorded. The average return for this intake of iron would be 33 gm. hemoglobin for 5 days, but this dog is more active than the average and might put out during 1 week iron feeding of 400 mg. Fe daily, 45 to 60 gm. new hemoglobin—compare with the result of liver feeding. The question of reserved storage and intestinal absorption comes in and we have, unfortunately, no figures for the red marrow iron content, so we must not push this analysis too far.

TABLE 3.—IRON CONTENT OF PERFUSED TISSUES OF NORMAL DOGS ON VARIOUS DIETS (AFTER BOGNIARD AND WHIPPLE).

Dog No.	Type of diet.	Duration, days.	Fe in mg. per 100 gm. of perfused fresh tissue.							
			Liver.	Spleen.	Rib.	Kidney.	Pancreas.	Heart.	Psoas.	Lung.
30–174	Standard salmon bread	31	20.4	38.0	22.8	4.7	2.4	6.5	6.3	10.2
30–250	Standard salmon bread	21	22.7	40.1	20.5	6.9	2.5	3.7	2.8	6.7
30–125	Kennel + iron (500 mg.)	31	17.1	86.8	17.5	4.0	1.6	3.3	4.3	13.4
30–103	Liver (300–450) + meat and bread	30	30.3	46.1	14.4	5.4	2.0	4.0	2.4	6.1
30–270	Carrot and mush	25	42.2	53.6	14.9	5.0	3.2	...	3.9	5.5
X–2806	Kennel	30+	13.9	23.3	7.9	2.2	1.6	3.0	3.4	3.7
X–2884	Kennel	30+	25.7	37.8	7.4	4.0	1.3	2.9	3.1	2.7
	Averages		24.6	46.5	15.0	4.6	2.1	3.9	3.7	6.9
	IRON CONTENT OF PERFUSED TISSUES OF ANEMIC DOGS.									
30–271*	Anemia level = 50–60% Hb.	30	5.0	17.5	4.1	1.4	0.7	2.9	4.0	3.3
30–257*	Anemia level = 50–60% Hb.	45	4.0	6.6	3.5	2.9	1.1	2.5	3.3	2.1

* Diet of bread, milk, rice, potatoes, salmon and onion, until perfusion.

Table 3 gives for convenient reference the condensed tabulated data from the experiments by Bogniard and Whipple.[2] The iron storage in various normal dogs on a variety of diets is in conspicuous contrast with that of the anemic dogs. It is obvious from the experiments in Table 3 and from those given above in this paper that an anemic dog is slowly depleted of its iron stored in the liver, spleen and marrow. The depletion is not complete as a result of 1 month's anemia and even 6 weeks will not completely reduce this reserve to the base line beyond which these tissues will not

give up iron under any condition of stress. A 2 or 3 months' anemia at about a 50% hemoglobin level will reduce these dogs to a relatively constant base line for iron contained in viscera, muscles and marrow (Table 1).

It seemed desirable to ascertain just how far the body depletion of iron could be carried and whether under these conditions the body could form any hemoglobin. It had been found (Table 5) that the striated muscle in its total mass contained a considerable store of parenchyma iron, and it was suspected that in a great emergency the body might draw on this store. It had been observed in this laboratory[5] that the anemic dog, during a 2 weeks' fast, could produce 40 to 60 gm. new hemoglobin which obviously must come from materials stored in the body. Furthermore it had been found[14] that certain amino acids given with the salmon bread diet would cause a considerable increase in the output of new hemoglobin (30 to 40 gm.) in these standard anemic dogs, and obviously iron must be drawn from some source to account for this new hemoglobin.

TABLE 4.—HEMOGLOBIN PRODUCTION IN DOG ON WHITE BREAD LOW-IRON DIET. EFFECT OF AMINO ACIDS AND FASTING.

Dog 33–85, female, adult, mongrel hound.

Diet periods 1 week each. Food, grams per day.	Food cons., %.	Wt., kg.	Plasma vol., ml.	Blood Hb., %.	Hb. remov., gm.
Wh.Br. 250, salm. 100, Kl. 20 . . .	89	16.9	1,025	41	11.4
Wh.Br. 250, salm. 100, Kl. 20 . . .	85	16.8	985	47	1.4
Wh.Br. 250, salm. 100, Kl. 20 . . .	100	16.2	995	57	11.1
Wh.Br. 350, salm. 150, Kl. 20, CLO 10	100	16.6	910	47	1.4
Wh.Br. 350, salm. 150, Kl. 20, CLO 10	100		965	43	13.5
Wh.Br. 350, salm. 150, Kl. 20, CLO 10	75	17.2	1,010	47	10.3
Wh.Br. 250, salm. 150, Kl. 20, CLO 15	82	17 0	945	41	11.0
Wh.Br. 250, salm. 150, Kl. 20, CLO 15	96	16 6	990	43	1.3
Phenylalanin 1 + glycin 1* . . .	100	17.0	960	46	9.5
Phenylalanin 1 + glycin 1* . . .	100	16.8	945	36	25.3
Phenylalanin 1 + glycin 1* . . .	100	16.9	980	42	11.4
Wh.Br. 250, salm. 150, Kl. 20, CLO 15	100	16.9	1,025	33	11.5
Glutamic acid 1*	100		1,085	38	1.1
Glutamic acid 1*	100	17.4	1,010	44	1.3
Wh.Br. 250, salm. 150, Kl. 20, CLO 15	100	17.3	960	55	12.7
Wh.Br. 250, salm. 150, Kl. 20, CLO 15	100	17.3	970	48	11.3
Fasting	0	15.4	880	39	8.9
Fasting	0	13.9	855	48	1.3
Wh.Br. 250, salm. 150, Kl. 20, CLO 15	86	14.8	880	45	1.3
Wh.Br. 250, salm. 150, Kl. 20, CLO 15	100	15.4	890	43	1.3

Wh.Br. = white bread; Kl. = dried skimmed milk; salm. = canned salmon; CLO = standard cod-liver oil.

* Wh.Br. 250, salm. 150, Kl. 20, CLO 15.

The experiments in Table 4 are of much interest and show that the body iron can be so depleted that the dog will no longer put out new hemoglobin during fasting or amino acid feeding periods. Under these conditions the body cannot supply or find any reserve iron, and in the face of a severe anemia it can produce only about enough hemoglobin to make up for the wear and tear of the circulating red cells. The factor x for red cell wear and tear is an unknown but is always present and has called forth much speculation—this comprehends the life cycle of the red cell.

Dog 33–85 (Table 4), a fairly active, slightly fat female mongrel hound, weighing 15 kilos, had been maintained at a hemoglobin level of 40 to 60% for 3 months on a diet of hospital table scraps. This dietary régime* was gradually shifted during a period of 2 months to the white bread diet low in iron, the anemia level being maintained. This dietary régime was continued for another 2 months, the animal's standard hemoglobin output being determined at the level of 45 to 55% hemoglobin.[17] The last weeks of this experiment are outlined in Table 4. The perfusion was done as usual and the final red cell hematocrit at the end of the perfusion read 1.7%.

Dog 33–85 shows (Table 4) during the tabulated first 8 weeks on this white bread diet low in iron an average weekly output of 7.5 gm. hemoglobin. It is recalled that a long anemia period of about 6 months preceded the experiments in Table 4, during the last 2 months of which the white bread diet low in iron was fed, so that there could be no assumed iron reserve store. This low iron diet contains about 5 mg. Fe in a day's intake. When phenylalanin and glycin are given, 1 gm. each per day for 3 weeks, we see a definite increase above the base line of about 29 gm. hemoglobin including the carry over into the subsequent bread control week. When glutamic acid is given there is no increase and actually less than the basal output on the bread alone. Fasting causes no increase and finally, during the last 2 weeks on the basal bread ration, the output is zero or less—that is, the body can form no new hemoglobin above the amount needed to make up for wear and wastage. Presumably the iron limitation is causing a definite limitation of hemoglobin production during fasting. This probably means that even on the salmon bread diet there is a little reserve of iron in the body which can be used in this fasting emergency, but with a very low iron intake and the utilization of the small iron reserve by amino acid supplement, this small reserve is exhausted and fasting gives no further hemoglobin production.

In this connection we observe in Table 5 that the parenchyma iron of striated muscle (Dog 33–85) is an average *normal* as is the *muscle hemoglobin*, showing that even in this emergency of extreme iron depletion these muscle tissues do not contribute iron to any appreciable degree.

* Dr. F. S. Robscheit-Robbins kindly directed the standardization and amino acid feeding of this animal.

This dog (33–85) also shows (Tables 1 and 2) the expected low values for parenchyma iron in the liver and spleen. The values for the viscera are similar to others in the same tables and show no depletion of iron below the usual base line. The low figure for the pancreas (0.7 mg. % Fe) is to be explained by edema. The rib analysis unfortunately was lost.

In this dog (33–85) the spleen was extracted carefully to ascertain the amount of Fe contained in red cells held in the spleen sinusoids and pulp. The same procedure used for muscle hemoglobin showed that about 30% of the total iron was in hemoglobin within red cells.

Table 5 shows a number of interesting points relating to *tissue iron* within the body. This iron in the striated muscles is about equally divided between the muscle hemoglobin and the muscle parenchyma, but the parenchyma iron is a little more abundant in the heart muscle (57%) and the muscle hemoglobin iron a little more abundant in the voluntary striated muscle (59%). Theorell[15] has shown that muscle hemoglobin contains 0.335% iron just as does blood hemoglobin, but the muscle hemoglobin molecule is much smaller.

TABLE 5.—MUSCLE HEMOGLOBIN AND MUSCLE IRON IN BLOOD-FREE TISSUES OF ANEMIC DOGS.

		Muscle hemoglobin.		Muscle tissue, Fe by analysis, mg. per 100 gm.	Parenchyma Fe by difference mg. per 100 gm.
Dog No.	Muscle.	Mg. per 100 gm.	Calc. equiv. as Fe, mg. per 100 gm.		
32–44	Heart	...	...	2.5	
	Psoas	...	...	4.5	
32–374	Heart	...	...	2.6	
	Psoas	...	...	2.7	
33–190	Heart	430	1.4	3.5	2.1
	Psoas	680	2.3	3.3	1.0
	Erector spin.	890	3.0	4.4	1.4
	Diaphragm	810	2.7		
27–235	Heart	345	1.2	2.9	1.7
	Psoas	320	1.1	3.0	1.9
	Adductor	340	1.1	3.4	2.3
	Diaphragm	400	1.3	3.2	1.9
33–85	Heart	410	1.4	2.6	1.2
	Psoas	550	1.8	3.1	1.3
	Adductor	500	1.7	3.1	1.4
	Diaphragm	880	3.0	3.2	0.2
33–325	Heart	390	1.3	3.3	2.0
	Psoas	615	2.1	3.3	1.2
	Adductor	525	1.8	2.9	1.1
	Diaphragm	675	2.3	3.5	1.2
33–92	Heart	...	...	2.5	
	Psoas	...	...	3.3	
33–1	Heart	...	...	2.5	
	Psoas	...	...	3.1	

Total muscle iron as distributed in muscle hemoglobin = 55%; in the parenchyma = 45%.

In this great emergency the body does not draw on this store of muscle hemoglobin and muscle parenchyma iron to manufacture new hemoglobin. As pointed out elsewhere[16] *activity* has vastly more influence on muscle hemoglobin than any other factor, and activity will mean high muscle hemoglobin even in the face of anemia. Likewise paralysis even with normal blood hemoglobin will mean rapid fall in the muscle hemoglobin. This perhaps is a fortunate independence of these factors relating to iron in the muscle and in the circulation, else an anemic animal might lose its power of motion or even the functional power of its heart.

Intravenous injection of colloidal iron does not modify in any way the store of iron in the muscles (Table 5).

Liver feeding causes a rapid and abundant production of new hemoglobin in this type of anemia and we record (Tables 1 and 2) the data related to iron distribution—Dog 33–325.

Dog 33–325 (Tables 1 and 2), a very active male mongrel poodle, weighing 10 kilos, was made anemic by bleeding as usual and maintained at a level of 45 to 60% hemoglobin for a period of 10 weeks. During this whole period the diet was of the white bread low iron type. The animal was then given 300 gm. of cooked pig liver in addition to the usual ration, and this was eaten. The next 3 days, however, the liver was refused, but on the 5th day the dog ate 300 gm. of raw pig liver over and above the regular diet. This supplement was refused on the 6th and 7th days. Therefore, on the 8th, 9th and 10th days the diet was supplemented daily with 4.1 gm. of a liver extract potent in secondary anemia (W1188—Lilly). This fraction[18] of 4.1 gm. was derived from 300 gm. of fresh liver and contained about 70% the potency of whole liver for hemoglobin regeneration in this type of experiment. On the 11th day the animal was perfused. The final red cell hematocrit after perfusion read 1%.

During the period of liver feeding 40 gm. of hemoglobin over and above the animal's customary production on the basal ration appeared in the blood stream, as can be seen below:

Dog 33–325.	Hb. level (%).	Plasma vol. (ml.).	Blood vol. (ml.).	Circulating Hb. (gm.).
At start of liver supplement	53	530	705	51.5
At end of liver supplement (at perfusion)	84	540	815	94.5
Increase in circulating Hb.				43.0
Hb. removed in sampling				1.4
Hb. produced due to basal diet (6 days)				5.0
Total net Hb. production due to liver feeding				39.4

This experiment (Dog 33–325) with liver feeding was not satisfactory because we wished for a maximal intake of whole liver during 4 or 5 days to be followed by the perfusion. This dog refusing the liver during several periods, enabled the body to mature completely the hemoglobin and red cells which might be related to the early liver intake and we see a large output of hemoglobin amounting to about 40 gm., which would be a reasonable return from this liver and liver fraction intake. The iron content of the liver shows

base line values and no increased storage. There may be a little more iron storage in the spleen but the muscles and other viscera show base line values. This all speaks again for a very rapid turnover of the iron as it comes in from the intestine.

*Intravenous Iron.** The accompanying paper shows that colloidal iron given intravenously to the standard anemic dog will be returned quantitatively within new formed hemoglobin. It seemed of importance to trace this iron within the body in these dogs.

Dog 33–1 (Tables 1 and 2), lean, fairly active female hound, weighing 12.5 kilos, was kept anemic for about 11 weeks at a hemoglobin level of 50 to 60%. During this time the diet was the ordinary kennel ration of hospital table scraps. A week on the white bread diet low in iron was followed by administration of colloidal iron intravenously, 54 mg. being given twice each day for 2 days (a total of about 215 mg.). The animal was perfused 23 hours after the last injection. The final red cell hematocrit following perfusion was 0.9%. The liver shows an iron content compatible with the average of *normal* dogs (Table 3), namely, 27 mg. Fe %. The spleen shows a figure close to the high values for *normal* dogs, which had received large oral doses of iron for a month (Dog 30–125, Table 3). The other organs show what might be regarded as anemia base line figures. Since about 122 mg. of iron can be accounted for in the liver and spleen, about 56% of the iron injected is demonstrated as stored in these organs. Histologic sections stained for iron show a heavy deposit of blue granules within the Kupffer cells of the liver.

Since it appeared that the liver and spleen were the only organs examined which seemed to be immediately concerned with the storage of the iron, and inasmuch as the *normal* storage of these organs had possibly been exceeded in the dose administered in the last experiment, it was decided to inject only as much iron as it was thought could be removed from the circulation by these two organs.

Dog 33–92 (Tables 1 and 2), a lean, quiet mongrel female hound, weighing 12 kilos, was made anemic and maintained for 3 months at a hemoglobin level of 40 to 55%. Following a week on the white bread low iron diet, this animal was given 54 mg. Fe per day for 2 successive days. Perfusion followed the last injection by 27 hours. The final red cell hematocrit following perfusion was 0.9%. Again all the organs, on analysis, show base line figures with the exception of the liver and spleen. The liver contained an amount of iron which was somewhat below that for an average *normal*, and the spleen contained an amount which was about an average for a *normal* dog (Table 3). The amount recovered in these two organs was about 75 mg. or about 70% of the amount injected. Histologic sections stained for iron show a definite deposit of blue granules within the Kupffer cells of the liver. Control sections from dogs fed iron showed no blue granules in the Kupffer or hepatic cells.

Iron recovery in these two experiments was not complete, the larger dose by vein, Dog 33–1, giving a 56% recovery, and the smaller dose, Dog 33–92, giving a 70% recovery. We were surprised that the marrow showed no evidence of iron storage. It is to be expected that most of the iron given by vein would be stored

* We are indebted to Dr. David Loeser of the Loeser Laboratory for the colloidal iron used in these experiments.

at first in the reticuloendothelial system, but it obviously varies somewhat and during these 3 days some material surely reached the mature stage of new hemoglobin and would not appear in the analyses. Some iron probably is to be found in the lymph glands and lymphatic tissue of the body, including the intestinal lymphatic tissue. Some iron is to be found in the plasma and perhaps in the whole blood in excess of the hemoglobin. Unfortunately no analyses of blood were made, but this omission is being corrected and in time, we hope, to account much more completely for the iron given by vein. It is, of course, a possibility that some iron may be washed out by this viviperfusion but this question can also be subjected to careful test.

It is interesting to note that in contrast to the results of Polson[12] there is no accumulation of iron in the lungs nor evidence of pulmonary emboli. His dosage was usually considerably higher than those used in these two experiments, but in view of the above data it would seem unlikely that the lungs function normally to conserve and store iron.

Discussion. The question of *red marrow* and its store of iron may well be debated. At present no dogmatic statements can be made but we may review some of the difficulties. This is one place in the body where iron may be concealed and leave the investigator in a quandary whether iron taken into the body may be here at all or whether in the form of parenchyma iron or of hemoglobin iron. We assume that marrow volume[7] is about two-thirds that of the liver but this area may be filled with red marrow or fat marrow or a mixture of the two.[11] In anemia the red marrow increases in bulk at the expense of the fat marrow, and after months of anemia the red marrow may replace completely all the fat marrow. There are great individual differences[11] and here is a large error confronting us if we figure the whole marrow on the basis of the rib analysis.

Method difficulties of iron analysis in bones has been pointed out under Methods. It is possible that autolysis of marrow in the bones may overcome some of these difficulties.

Viviperfusion as used in these experiments introduces another factor which cannot at present be evaluated. If iron coming into the body is moved rapidly into the marrow it may be rapidly incorporated into the hemoglobin and protoplasm of the immature red cells whose increase would tend to push out the more mature red cells which as we know begin to appear in the circulation in considerable numbers on the 3d day after iron administration. These red cells about to emerge might be dislodged by the perfusion and be lost to the rib analysis, yet not being in the circulation before death would also be lost to the analysis of the circulating hemoglobin.

An attempt to extract and measure the hemoglobin in the red marrow of the various bones has not yet been made but we hope to accomplish this in the near future. Histologic sections of marrow give some help and show that a fair number of mature red cells

and large numbers of nucleated red cells are always to be found in the red marrow. The marrow capillaries may be visible and pretty well freed of red cells but the red cells outside of these spaces in the interstitial areas are of course out of reach of any perfusion. Attempts to subdivide the total red marrow iron into parenchyma iron and hemoglobin iron face obvious difficulties, but in time we should have some data of real value.

Parenchyma iron is of some interest in these experiments and its uniformity deserves mention. After the iron stores are depleted by anemia for many weeks we see that the kidney, pancreas and even liver when bloodfree, contain only 1 to 2 mg. Fe per 100 gm. fresh tissue. It is perhaps surprising that the liver should give up all but this small measure of Fe. When we recall that all protoplasm contains Fe[8] we may look at this parenchyma iron as perhaps incorporated in the cell protoplasm and necessary for its life and function. The *spleen* may be reduced to about 8 mg. Fe per 100 gm. fresh tissue, and if we allow about 3 mg. for the contained hemoglobin we have left 5 mg. Fe as the base line for parenchyma iron.

Red marrow of the rib is usually made up of cells and contains no fat marrow. We may accept 5 mg. Fe per 100 gm. bone, and allowing two-thirds of the rib weight as bone we have a marrow content of 15 mg. Fe per 100 gm. red marrow. Further we may allow 5 mg. for contained hemoglobin iron which value probably is too high, but at any rate 10 mg. or more Fe per 100 gm. red marrow is a much higher level for parenchyma iron than any other tissue.

Muscle parenchyma iron should be mentioned and includes heart and skeletal muscles. The average iron content (Table 5) is 3.1 mg. Fe per 100 gm. fresh tissue, and this is divided roughly 45% parenchyma iron and 55% muscle hemoglobin iron. This gives about the same average value for parenchyma iron in the muscles as in liver, kidney and pancreas. It is of significance that in the face of long continued severe anemia and urgent need for iron from any available source, the dog does not draw on either the muscle parenchyma iron or the muscle hemoglobin iron. Conversely when iron is given in abundance by mouth or by vein a surplus is not stored in the muscles. A 10-kilo dog will have 2500 to 4000 gm. of striated muscle, and this means 80 to 125 mg. Fe. This is to be compared with the stores of Fe found elsewhere in the non-anemic normal dog of 10 kilos weight. The dog will have a circulating blood volume of about 900 cc., containing about 180 gm. hemoglobin or the equivalent of 600 mg. Fe. According to Table 3 there would be in reserve in the liver about 90 mg. Fe and in the spleen only about 12 mg. Fe. The reserve in the red marrow is largely guesswork but might amount to 30 to 50 mg. Fe. The dominance of the liver in reserve iron storage is obvious.

Absorption of iron from the intestine is influenced by many factors but we have no evidence that there is any difference in the dog due

to the ferrous or ferric state of the iron. The absence of bile does introduce a factor influencing iron absorption and there are probably a host of factors which bear on this point of the absorption of iron contained in the food.

It has been reported by several investigators[3, 4, 6] that the ingestion of large daily doses of iron is followed by a decrease in blood phosphorus and may result in a severe rickets or even death. The mechanism for such a reaction would seem to be the formation of insoluble Fe and P compounds in the intestine, these being excreted as such at the expense of the body's supply of phosphorus. If this is true it is logical to suppose that normally something approaching the converse takes place, with reference to the absorption of iron. The average diet often contains 50 to 60 times the weight of P as compared with Fe.

Iron given intravenously to the anemic dog will eventually be returned quantitatively in new hemoglobin and red cells, and we can account for 100% of the injected Fe as seen in Tables 5 and 6 (preceding article).[1] Yet when we attempt to trace and account for this iron (Tables 1 and 2) a day or two later we find but 55 to 70%. Obviously it must be in the body in some form or other. Various possibilities have been discussed related to the red marrow particularly, but we have not as yet excluded the possibility of some iron circulating in the blood other than hemoglobin iron and the usual plasma iron.

Summary. Reserve iron storage in the dog can be exhausted during 2 to 3 months by a continuous anemia with hemoglobin level maintained at one-half to one-third of normal. Given this elimination of reserve iron we may attempt to trace iron given by mouth or vein.

A *rapid turnover of iron* is the conspicuous feature of the experiments dealing with iron given by mouth and short feeding experiments (1 to 2 days) give no evidence of any iron store in the liver. As the iron feeding experiments are lengthened we see a variable accumulation of iron in the liver, but the amounts are small and a very rapid appearance of the iron in matured hemoglobin is the conspicuous feature.

The importance of bloodfree organs is stressed, and other method difficulties are discussed.

Parenchyma iron of various bloodfree organs is relatively a constant in these dogs. Liver, kidney and pancreas average 1 to 2 mg. Fe %. The lung is a little higher, or 3 mg. Fe %. The spleen is still higher, or 5 to 6 mg. Fe %. The red marrow apparently has the highest level of parenchyma iron—an uncertain figure but probably in excess of 10 mg. Fe %. The striated muscles actually rate with the liver and kidney, although the average for total contained iron is 3.1 mg. Fe %. About 1.6 mg. Fe is muscle hemoglobin iron, leaving the parenchyma iron as 1.5 mg. Fe %.

Muscle hemoglobin iron and muscle parenchyma iron are inviolate stores of iron which are not drawn upon no matter how great is the emergency due to anemia. Conversely no surplus iron can be demonstrated in this tissue where iron is given intravenously.

Iron depletion can be carried to a point where there is almost a complete cessation of hemoglobin production in a standard dog on a diet very poor in iron (Table 4).

Intravenous iron in the doses given will result in large storage in the liver and spleen—55 to 70% of the total Fe given. We are not prepared to say where the remaining iron is to be located in the body tissues or fluids but it certainly is not eliminated.

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THE AFTER-HISTORY OF LIPOID NEPHROSIS.*

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The condition known as lipoid nephrosis, or chronic nephrosis, has been the subject of much controversy the past few years. Our interest in the condition began 10 years ago when we studied a patient and later followed him to autopsy. This case was reported in 1925. Since that time we have had the opportunity to study 7 additional cases presenting this unusual syndrome. Two of these patients, leaving the hospital after marked improvement, disappeared from view and we have been unable to trace them. The other 5 patients have been kept under constant observation and their subsequent course recorded. This makes a total of 6 cases which have been followed with reasonable care and persistence.

It is not the intention of this paper to review the arguments for and against the use of the term nephrosis, or whether the isolation of this syndrome as a distinct type of nephritis is justified. It is also not our purpose to discuss whether this is only a masked form of glomerulonephritis, or whether we are justified in calling it diabetes albuminurica. This entire controversy was very ably discussed by Christian in 1929, and the articles which have appeared since his review have not aided materially in solving the problem. Christian collected 18 adult cases with autopsy, the average duration being 8.8 months. He adds, "Clinical reports indicate frequent recovery, but the literature is devoid of much in the way of follow-up of these cases in later years to see whether or not their apparent cure is complete or not." In reviewing the literature we have noted that certain cases were reported after a very brief observation, and notes on the subsequent course of the history were lacking, while other cases had been seen in the terminal stage and were reported with autopsy findings. For this reason we thought a record of our cases might be of some interest, for, although small in number, 1 of the patients has been followed for 8 years, 2 for 4 years, and 1 for 3 years.

In the diagnosis of this condition we have applied the usual clinical and laboratory criteria. All these patients have shown marked edema, normal blood pressure, absence of cardiac enlargement, heavy albuminuria, high blood cholesterol, low blood proteins, usually with inversion of the albumin-globulin ratio, and a diminished basal metabolic rate. We have excluded 4 patients who were

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thought at first to have lipoid nephrosis, but after observation of a few weeks showed an increasing nitrogen retention with an accompanying increase in blood pressure. Three of these patients were diagnosed as chronic nephritis and the diagnosis later verified by pathologic findings. One patient showed at autopsy amyloid kidneys. A brief summary of our patients diagnosed as lipoid nephrosis is as follows:

Case Reports. CASE 1.—Male, aged 34, was admitted to the University of Kansas Hospital on July 3, 1924, and dismissed on August 5, 1924. This patient suffered from marked edema of the legs and abdomen. The heart was not enlarged on physical examination; roentgenogram showed its outlines to be within normal limits. The patient's blood pressure was normal throughout the period of observation, the systolic pressure varying from 135 to 145, diastolic from 90 to 100. Patient's blood cholesterol on 3 examinations was 344, 366 and 242; blood urea on 3 occasions was 14, 10 and 6; serum albumin on admission was 2 gm. per 100 cc.; serum globulin, 4 gm. per 100 cc.; phenolsulphonephthalein test, 22% in 2 hours. The urine showed very heavy clouds of albumin and on microscopic examination numerous cholesterol crystals. The basal metabolic rate was −10%; Wassermann and Kahn reactions negative. Death occurred 1 week after discharge.

At partial *autopsy*, examination of the kidneys and liver was permitted. The pathologic diagnosis was chronic interstitial nephritis with lipoid infiltration. There was a superimposed acute nephritis, but chronic glomerular changes were neither marked nor extensive.

The *histologic* report of the kidney sections is as follows: The picture in the kidney varies in different fields. In some places the glomeruli are intensely engorged with red blood cells and in others very few red cells are seen and the endothelial cells are swollen and filled with large vacuoles. Some are larger and show a tuft which is largely replaced by masses of fibrous tissue due to proliferation of the tissue about the Bowman's capsule. The tubules show a varying grade of degeneration, in some places nothing but cloudy swelling and in others considerable dilatation and pressure atrophy of the cells. Toward the medulla many of the cells show a peculiar change in that they are swollen and show a very markedly vacuolated cytoplasm suggesting a lipoid type of cells. In this region also there is marked proliferation of some of the cells in the collecting tubules with a desquamation presenting a picture somewhat suggestive of acute nephritis. There is some infiltration of large and small mononuclears throughout the stroma. The stroma is irregularly increased toward the cortex, showing a rather patchy distribution. Hyalin casts are present in many of the collecting tubules and a few of the convoluted epithelial tubules show vacuoles and cells of the cytoplasm suggesting a vacuolar type of degeneration or a lipoid change.

CASE 2.—Male, aged 30, was admitted to the University of Kansas Hospital on August 1, 1930, and dismissed on August 28, 1930. The patient at this time showed a very marked edema and a heavy albuminuria. His blood cholesterol was 420 mg., serum albumin 2.7, serum globulin 1, the blood chemistry otherwise normal. The basal metabolic rate −15%, the Wassermann and Kahn reactions negative. The patient was dismissed from the hospital much improved. He was readmitted on April 21, 1931, and remained until May 2, 1931. Phenolsulphonephthalein was 100% in 3 hours; blood cholesterol 400 mg. per 100 cc.; serum albumin 1.65; serum globulin 1.85. He was again admitted on May 5, 1931, and dismissed on May 27 with no essential change in the physical findings. March 15, 1932, he was again admitted into the hospital showing at this time blood choles-

terol 566, serum albumin 1.9, serum globulin 2.4, blood pressure 100 systolic, 80 diastolic. He was again dismissed improved. On later admissions (from June 21 to July 23, 1932, and from January 15, 1933, to April 21, 1933) he showed essentially the same picture. His last admission was on September 21, 1933, when he again showed a very marked edema, and now nitrogen retention, as well as an increase in blood pressure. The non-protein nitrogen on admission was 36 mg. per 100, on November 18, 1933, was 112, and creatinin rose from 1.2 to 2.1 mg. per 100 cc. The total blood proteins were consistently low, varying from 2.2 to 3.1 gm. per 100 cc. Death occurred on November 19. The day of death the non-protein nitrogen was 120 mg., urea 69 mg., creatinin 2.5 mg. per 100 cc. The patient's blood pressure, which on admission was 130 systolic, 80 diastolic, rose to 190 systolic and 122 diastolic on November 6.

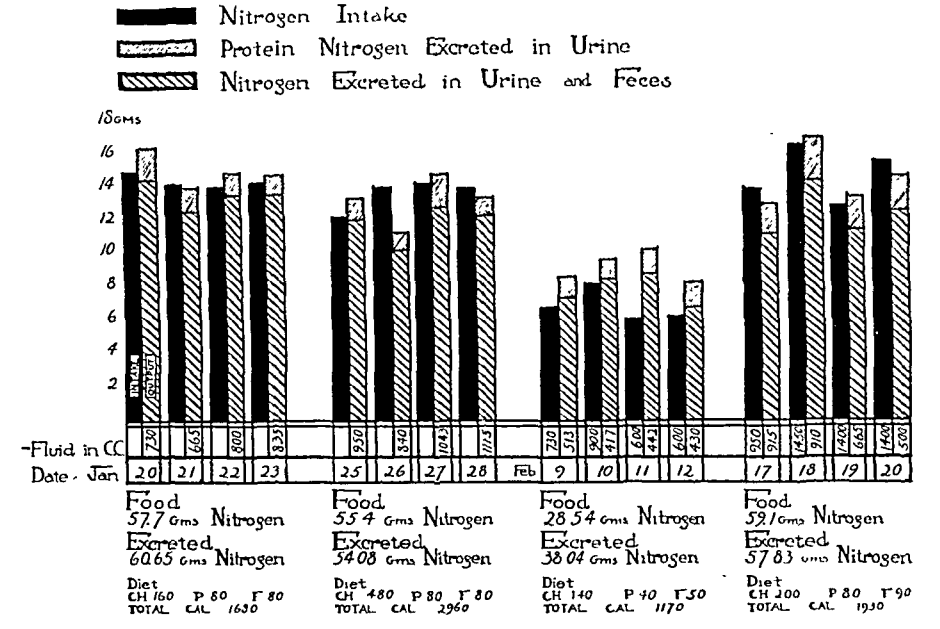


FIG. 1.—Studies of the nitrogen balance in Case 2.

Pathologic diagnosis: Chronic glomerulonephritis, with extensive fatty change, chronic myocarditis, chronic splenitis and perisplenitis; hydropic degeneration and chronic passive congestion of the liver; acute bronchopneumonia, and generalized anasarca.

The *histologic* report of the kidney sections is as follows: Most of the glomeruli are large but some appear shrunken. All of the tufts are avascular and fibrosed and show some degree of pseudolobulation. Frequently they are adherent to the capsule. Some appear cellular and contain a few polyps. A more striking change is the dilatation and degeneration of the tubules, especially the convoluted tubules which are considerably distended and vary some in size and shape. In some places the epithelial lining of the tubules is flattened and appears degenerated. The cells stain a deep pink and are considerably disintegrated though usually intact. Some desquamated epithelial cells are seen, however, in the lumen. In other areas the epithelium is swollen and presents a rather foamy vacuolated appearance. The nuclei are occasionally absent. There is a marked increase in the stroma and patches of fibrous tissue containing small, irregular tubules and infiltrated with mononuclears. Triangular, fibrotic areas containing

some hyalinized glomeruli are seen just beneath the capsule. An occasional hyalin cast is seen. The medulla is very congested and edematous in appearance. Many of the collecting tubules are dilated and a few contain hyalin casts. A few mononuclear cells are scattered throughout. Trichrome stains show a marked increase in the stroma with only remnants of epithelial tissue most apparent in the glomeruli. Fat stains show many fat droplets in the kidney tubules, especially the convoluted ones. There is very little fat elsewhere.

This patient was under observation 3 years.

These 2 patients were the only fatalities in our series.

CASE 3.—Female, aged 35, was admitted to the University of Kansas Hospital on March 5, 1927, complaining of marked swelling of the feet and abdomen, and remained until July 13, 1927. The edema in this case was extreme, and on one occasion both legs were punctured repeatedly with a hypodermic needle and in 4 hours 2 liters of fluid were collected. Her urine contained consistently large amounts of albumin and cholesterol crystals. The serum albumin on March 7 was 3.2 gm. per 100 cc. Basal metabolic rate was −6%; Wassermann and Kahn reactions negative. The blood pressure throughout her stay in the hospital varied from 130 to 140 systolic, and 80 to 90 diastolic; blood cholesterol varied from 258 mg. per 100 cc. to 625 mg. The values for non-protein nitrogen, urea, creatinin, chlorids and sugar were consistently normal. At the time of her dismissal from the hospital blood cholesterol was 300. This patient left the hospital much improved and was seen on November 4, 1927. At this time her urine showed a trace of albumin; blood pressure was 140 systolic, 95 diastolic; blood cholesterol 250.

Since leaving the hospital she has steadily improved, and was examined on November 28, 1934. At this time her blood pressure was 132 systolic, 94 diastolic. She appeared in perfect health; urine was negative for albumin and sugar. She was not aware of anything abnormal in her condition and considered herself in perfect health. This patient has been under observation 8 years.

CASE 4.—Female, aged 53, was admitted to the University of Kansas Hospital September 24, 1931, and dismissed December 10, 1931. This patient on admission showed very marked edema of the legs and heavy albuminuria. The blood cholesterol was 428 mg. per 100 cc., serum albumin 1.92, serum globulin 0.94 gm. per 100 cc. Phenolsulphonephthalein test showed 50% in 2 hours. The basal metabolic rate was −18%; Wassermann and Kahn reactions negative. The patient's blood pressure during her stay in the hospital varied from 120 to 140 systolic and 90 to 95 diastolic. The edema cleared up during her stay in the hospital and on December 5, 5 days before dismissal, her blood cholesterol was 441 mg. per 100 cc., serum albumin 2.48, and serum globulin 1.90. Patient was seen on June 14, 1932, at which time the urine contained a faint trace of albumin, not enough for quantitative estimation. On July 13, 1932, the urine was negative for albumin and also again on October 3. On January 11, 1932, the patient's urine was negative for albumin and sugar, specific gravity was 1.020, blood cholesterol 208 mg., serum albumin 4.9, serum globulin 1.9. On October 9, 1933, urine was normal, blood cholesterol 283, serum albumin 4.4, serum globulin 2.6. Since that time the patient's blood and urine have been repeatedly examined, last examination being February 6, 1935, when the urine was normal, the blood cholesterol 236 mg. per 100 cc., total blood proteins 6.32 gm. per 100 cc. At the present time she is apparently well. This patient has been under observation 4¼ years.

CASE 5.—Male, aged 17, entered the University of Kansas Hospital first on July 9, 1931, and was dismissed on March 24, 1932. He showed the

usual picture of marked edema and heavy albuminuria. The basal metabolic rate was −14%, the Wassermann and Kahn reactions negative. Blood cholesterol during this admission varied from 460 to 263 mg. per 100 cc. On admission the blood cholesterol was 263 mg. serum albumin 1.5 gm. and serum globulin 4.9 gm. per 100 cc. During this admission the blood cholesterol at one time rose to 536, serum albumin fell as low as 1.6 and the serum globulin to 2.7. Phenolsulphonephthalein test on admission was 60% in 2 hours. The blood pressure varied from 110 to 130 systolic, and 75 to 85 diastolic. The patient was dismissed on March 24, 1932, blood cholesterol at this time being 267 mg., serum albumin 3.5 and serum globulin 3.37. He was readmitted on June 3, 1932, and dismissed December 21, 1932. The edema during this stay was much less marked. At the time of his dismissal the blood cholesterol was 193 mg. per 100 cc., serum albumin 4.15, and serum globulin 2.9. This patient has constantly improved since his return home. On February 15, 1934, his blood pressure was 120 systolic, 75 diastolic; physical examination revealed nothing abnormal. The examination of urine at this time was negative. It contained no albumin, no sugar, and no casts on microscopic examination. The patient considers himself well and is so considered by a colleague who now has him under observation. This patient has been under observation 4 years.

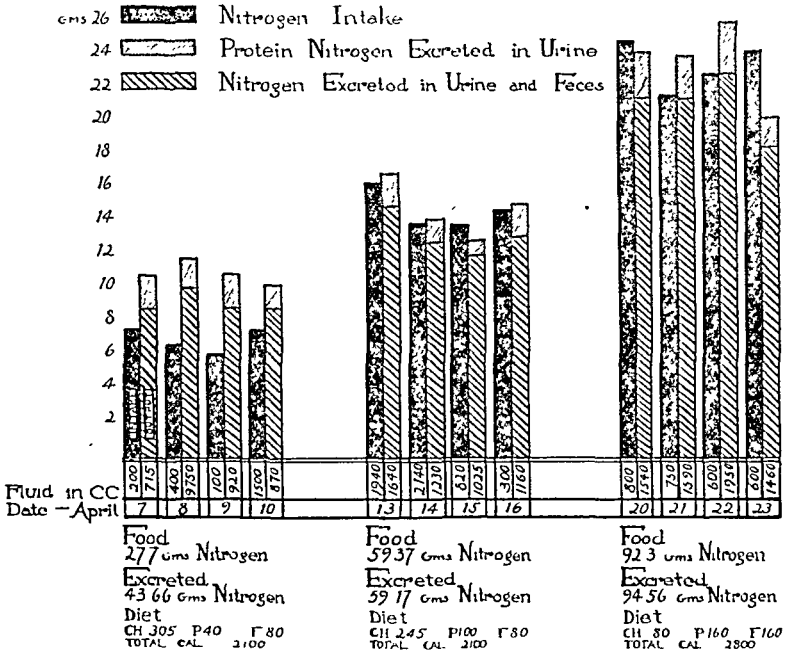


FIG. 2.—Studies of the nitrogen balance in Case 6.

CASE 6.—Male, aged 19, was admitted to the University of Kansas Hospital on February 26, 1932, and discharged April 2, 1932. He showed a very marked edema. Blood cholesterol on admission was 882 mg., serum albumin 1.83 gm., serum globulin 0.6 gm. per 100 cc., with a marked albuminuria. The patient's blood pressure varied during this stay from 120 to 130 systolic and 80 to 90 diastolic. Basal metabolic rate was −18%; Wassermann and Kahn reactions were negative. He was dismissed much improved; but was again in the hospital from November 23 to December 1, 1932, showing essentially the same picture as on first admission. He was again admitted for observation on April 2, 1933, and dismissed on April 24,

1933. Patient was readmitted October 19, 1934, for observation, and was dismissed on October 28, 1934. During this admission he showed a blood cholesterol of 157, serum globulin 3.1. Phenolsulphonephthalein test showed 85% in 2 hours. The urine still contained a heavy cloud of albumin. Patient's last period of observation was from January 22 to January 25, 1935, when he was admitted suffering from acute pharyngitis. At this time he showed no edema. His blood pressure at this time was 120 systolic, 80 diastolic, blood cholesterol 218 mg., serum albumin 5.4, serum globulin 3.2. On examination of the urine, one specimen contained no albumin, two other specimens contained a trace. The patient feels perfectly well, although the urine still shows albumin.

Summary. Six cases presenting the syndrome of lipoid nephrosis have been studied. Two of the patients died, both showing at autopsy marked acute glomerular nephritis with evidence of chronic glomerular changes. Four of the patients are alive, 3 of them are clinically well, 1 appears in good health and still shows a definite but not constant albuminuria. The 3 patients who have apparently recovered have been under observation 8 years, 4½ years and 4 years. The patient who has recovered except for a slight albuminuria has been under observation 3 years.

A few words regarding the therapy in these cases may be of interest. We have employed at one time or other practically every method of treatment recommended, including high protein diets, blood transfusions, intravenous glucose, thyroid extract, parathormone, various diuretics including novazurol and salyrgan.

We have given our patients from 70 to 100 gm. of protein daily. Very high protein diets in our experience present a difficult problem. Studies of the nitrogen balance in 2 patients also indicated that an excess of protein intake was not stored but excreted as urinary nitrogen (Figs. 1 and 2).

Blood transfusions and intravenous glucose injections were apparently of temporary value at least. We have not found thyroid extract or parathormone of any definite value. Bacterial antigens were of questionable value. We have seen no detrimental effects from the use of novazurol or salyrgan. At times they produce abundant diuresis, at other times no apparent effect. One patient (Case 2), was given intravenous gum acacia and a few days later developed an acute nephritis with exitus. This may, of course, have been merely a coincidence.

The last 3 patients have been placed on a very high carbohydrate diet from 600 to 800 gm. daily, occasionally as high as 1000 gm. They have improved remarkably, either as a result of the diet or because of the healing powers of nature.

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HYPERPARATHYROIDISM WITH RENAL INSUFFICIENCY.

REPORT OF A CASE.*

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THE coëxistence of tumor of the parathyroid bodies and pathologic changes in the kidneys was recorded by McCallum,[1] in 1905, and has since been encountered by pathologists with considerable frequency. The recent advance in knowledge of the functions of the parathyroid glands has now provided an explanation, based on the known disturbances in mineral metabolism which accompany parathyroid dysfunction, for this combination of circumstances. Originally a matter of interest to pathologists, the association of renal and parathyroid lesions now concerns the clinician as well, since the awareness of this relationship has often led to the early diagnosis of hyperparathyroidism. Albright and his colleagues[2] have divided the renal lesions in hyperparathyroidism into three types. Type I consists of pyelonephritis secondary to the formation of calcium phosphate stones in the renal pelves. To Type II belong the cases with deposits of calcium in the renal parenchyma, and to Type III those patients showing signs of acute parathyroid poisoning with anuria. The frequency with which Type I lesions occur in this condition is now generally appreciated. The second type of renal complication of this disease, however, the diffuse calcification of the renal parenchyma without calculi in the kidney

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† Aided by a grant from the Commonwealth Fund.

pelvis has been frequently described by pathologists, but the clinically detectable disturbances attributable to it, though recognized,[2,3] are less well delineated.

The present communication describes a patient, proved to have the classical syndrome of hyperparathyroidism, with parathyroid tumor, osteitis fibrosa cystica and diffuse calcification of the kidneys, whose disease escaped detection for an unknown period because the observed disturbances in renal function were regarded as arising from an atypical form of chronic glomerulonephritis. Removal of the tumor has been followed by disappearance of all evidence of hyperparathyroidism. Detailed studies of renal function before and after parathyroidectomy indicate, however, that no significant change in the renal findings has occurred.

TABLE 1.—BLOOD AND URINE DATA OF CASE REPORTED.

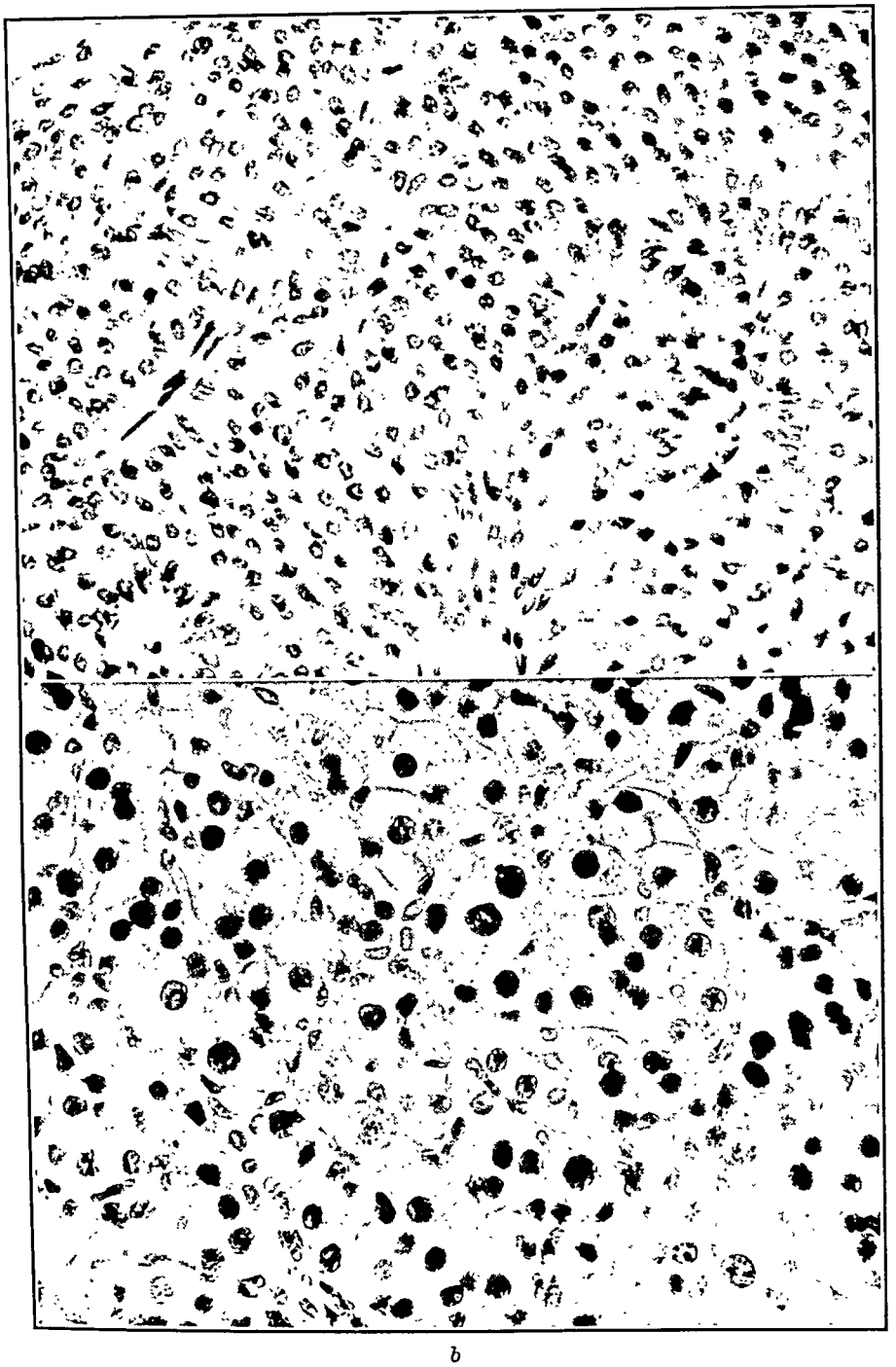
	Normal.	1/18/31.	2/22/31.	5/5/31.	5/28/31.	9/20/31.	1/16/35.	1/17/35.	4/3/35.	4/4/35.
B. U. N., mg./100 cc.	15 0	31 3	37 2	33 4		20 4	24.3		21.4	
Plasma protein G/100 cc.	7 0		7.7			7.6			7.48	
Urine volume, cc./12 hrs.*	380	666	631	745		377	605		810	
Specific gravity after fluid restriction*	1 025	1 010	1 010	1 009		1.010	1.010		1.010	
Reaction	Acid	Acid	Acid	Acid	Acid	Acid	Alk.		Acid	
Protein, mg./12 hrs. . .	100 or less	13	202	111		30	72		154	
Casts, per 12 hrs. . . .	5000 or less	0	10,500	58,000		0	3300		4500	
R. B. C., millions/12 hrs. .	0.5 million or less	0 62	0.76	1 1		0.25	0.03		0.53	
Urea clearance (12 hr.) % of normal† . . .	100%	27	23	21	18‡	28	27		36	34‡
Glomerular filtr., cc./min.§	100 cc. per min.				28			42		44

* The technique of Addis[24] was followed in the concentration test and sediment count.
† Comparison of 12- and 2-hour urea clearances to be published by Landis et al.[25]
‡ Two-hour urea clearances by the Van Slyke technique.
§ Measured by the creatinin method of Rehberg.[26]

Case Report. Miss M. F. (U. H. No. 34-16812), aged 35, a trained nurse, reported to one of us (F. C. W.) in January, 1934, for a periodic health examination. As a girl she was unusually athletic, engaging in the most strenuous forms of exercise without difficulty. She enjoyed good health from 1920 to 1923 while she was a student nurse. When first seen she was actively engaged in visiting nursing, as she had been for the past 7 years. Although able to carry on her work, she had not felt well for several years. Since 1930 there had been increasing lassitude, and fatigability. In 1931 or 1932 polyuria, polydipsia and nocturia appeared. She drank 12 to 15 glasses of water a day and 2 to 3 at night. Severe constipation required a daily enema. From 1932 to 1934 several attacks of fleeting joint pains occurred in the feet, ankles and elbows, associated with slight swelling but no redness of the involved joints. Yearly examinations of the urine, begun elsewhere in 1928, had revealed slight albuminuria and cylindruria. The specific gravity of the urine did not exceed 1.010.

FIG. 1

a



b

(*a*) Section from the right upper parathyroid gland showing normal structure. (× 540.)

(*b*) Section from the parathyroid adenoma showing "Wasserhelle" cells. (× 540.)

A secondary anemia was present. The basal metabolic rate was −12% in 1932. Thyroid therapy for a few months gave some relief from the asthenia. A low-protein diet was also prescribed at this time. Most of the teeth were removed in 1932 following a severe gingivitis. No history was obtained of previous nephritis or of scarlet fever. Upper respiratory infections had been infrequent and mild. The weight was 128 pounds in 1931 and 94 pounds in 1933. In view of the reported urinary abnormalities, tests of renal function were carried out in January and February, 1934, with results shown in Table 1, which led to a diagnosis of chronic diffuse glomerulonephritis. In May, 1934, the patient was admitted to the medical clinic of this hospital for more extensive study.

Physical Examination (May 5, 1934). Height, 60¼ inches. Weight, 97½ pounds. Blood pressure 110/80. The skeleton was unusual in that the head was disproportionately large, and the lower extremities were somewhat underdeveloped. The skin was sallow and the mucous membranes pale. The eye grounds were entirely normal. All but two teeth had been removed. The tonsils appeared to be infected. A soft systolic murmur was heard over the heart, which was normal in size and configuration. Physical examination was otherwise normal.

Laboratory Examinations. Erythrocytes numbered 3.8 million; hemoglobin, 66% (Sahli). Blood smears were normal except for moderate anisocytosis and poikilocytosis. Repeated urine examinations disclosed a specific gravity which varied between 1.005 and 1.010. There were traces of albumin in all specimens examined. No erythrocytes were observed. The average voluntary daily fluid intake was 2100 cc., the urinary output 1350 cc. Phenolsulphonephthalein elimination was 33% in the first hour, 15% in the second. Further renal functional tests are shown in Table 1. Blood sugar was 92 mg. per 100 cc. The basal metabolic rate on 2 occasions was −15% and −22%. Serum cholesterol was 424 mg. per 100 cc. Electrocardiogram revealed a *P–R* interval of 0.23 second, but was otherwise normal.

Course in the Hospital. The tonsils and the two remaining teeth, both infected, were removed. In view of the history of polyuria and polydipsia, a Roentgen ray examination of the head was made which revealed abnormal osteoporosis of the skull, suggesting the possibility of hyperparathyroidism. Investigations to test this possibility showed that all essential criteria were satisfied. Serum calcium was 15 mg. and serum phosphorus 2.7 mg. per 100 cc. Blood phosphatase liberated 0.24 mg. phosphorus per cc. of serum. Roentgen ray examination of the bones showed localized areas of bone destruction with cyst formation in the pelvis, spine, femora, humeri and bones of the hands. There was considerable cupping of the bodies of the vertebræ. Roentgen ray examination of the abdomen showed diffuse mottled opacities in the region of both kidneys. An intravenous urogram revealed no stones in the renal pelves. A diagnosis of hyperparathyroidism with osteitis fibrosa cystica and parenchymal calcification of the kidneys was made. The patient was transferred to the Surgical Division and an operation was performed on May 29, 1934.

Operative Findings. Examination of the posterior aspect of the right lobe of the thyroid gland revealed a yellowish body approximately 5 by 7 by 2 mm. situated immediately below the superior pole, near the medial border of the gland. Biopsy specimen was identified in frozen section as parathyroid tissue and the nodule was removed. In a corresponding position on the left side a normal-sized parathyroid gland was identified but not removed. Careful search below the inferior pole of the left lobe revealed an encapsulated yellow mass approximately 20 by 10 by 10 mm. closely attached to the inferior thyroid vessels and the recurrent laryngeal nerve and situated almost behind the clavicle at the sterno-clavicular junction.

This proved to be a parathyroid adenoma on microscopic examination, and was completely removed.

Photomicrographs of the tissues removed at operation are shown in Fig. 1.

Postoperative Course. On the day before operation serum calcium was 18 mg. per 100 cc.; 21 hours after operation it had fallen to 13 mg. and 7 hours later to 11.5 mg. per 100 cc. On the 2d and 3d postoperative days it was 10.4 mg. per 100 cc. A week after operation serum calcium was 8 and serum phosphorus was 4 mg. per 100 cc. Three days later the patient experienced paresthesias in the face and extremities, became very apprehensive, and developed severe tetany, which was relieved by intravenous administration of calcium gluconate and parathyroid hormone. Within a few days after operation the patient became free of polyuria and polydipsia. As soon as she was ambulatory she stated that she felt better than at any time in the past 5 years. A concomitant improvement in her mental outlook was equally striking. High-calcium diet with viosterol was prescribed, and the patient left the hospital on July 3, 1934, at which time serum calcium and phosphorus were 9.4 and 4.4 mg. per 100 cc., respectively. Two weeks later she omitted the usual doses of calcium because of nausea, and again developed mild tetany which was controlled with calcium gluconate given intravenously. From that time until the present (April 30, 1935) there has been a steady improvement. Gain in strength has continued until the patient now feels entirely well. The intractable constipation has entirely disappeared. There has been a gain in weight of 11 pounds. On February 20, 1935, the basal metabolic rate was +7% and the serum cholesterol was 310 mg. per 100 cc. Frequent analyses have shown the serum calcium and phosphorus to be normal. Blood phosphatase liberates 0.14 mg. of phosphorus per cc. of serum.

The renal and osseous lesions have not shown comparable improvement. Table 1 contains data which indicate that there has been a slight but probably insignificant increase in renal function since removal of the tumor. Roentgen examination made on April 3, 1935, showed that the bones were essentially unchanged in appearance. The calcium deposits in the kidneys were likewise unaltered. The patient resumed her full duties on September 1, 1934, and has continued them uninterruptedly up to the present.

Discussion. In considering the pathogenesis of the present case, we have taken the prevailing view that a parathyroid tumor is responsible for evidences of hyperparathyroidism, and that calcium deposition in the kidneys is a consequence of the disturbed mineral metabolism which characterizes that condition. Hypercalcemia and an unusually high concentration of calcium and phosphate in the urine, which occur both in experimental and clinical hyperparathyroidism, have been regarded as the factors responsible for the deposit of calcium in the kidneys. The suggestion has been made that since the renal cells elaborate urine which is distinctly acid, the reaction within the cells is, in consequence, more alkalin than that of the blood, which condition predisposes to intracellular precipitation of calcium phosphate. This conception, however attractive, does not rest, as far as we are aware, on direct experimental evidence. It is not easily reconciled with the observation that the calcium deposits in the kidney of hyperparathyroidism are very widespread,[4] occurring within the glomerular capillaries, the walls of the capsule of Bowman, and the capsular spaces and the lumina of the tubules, where, judging from evidence obtained from the

amphibian kidney,[5] the reaction is either that of the blood or is distinctly more acid. Whatever the mechanism concerned, however, it is an observed fact that the administration of excessive amounts of parathyroid hormone to dogs results in the deposition of calcium in the kidneys, and produces renal insufficiency.[6,7] This seems to us to warrant the assumption that an excessive secretion of parathyroid hormone in the human may likewise result in calcification of the renal parenchyma which ultimately alters renal function.

A different conception of the sequence of events is held by some writers. Hyperplasia of the parathyroid bodies, observed in chronic renal disease,[8,9] has been looked upon as evidence of the occurrence of secondary hyperparathyroidism. The relationship between chronic nephritis and enlargement of the parathyroids is not clear, but in the recent opinion of Pappenheimer and Wilens[9] and Smyth and Goldman[10] the kidney disease is regarded as primary, initiating a secondary and presumably compensatory hyperplasia of the parathyroids. The purpose of the compensatory reaction is presumably to correct the disturbed ratio of calcium to phosphorus in the blood of patients with severe nephritis where phosphate retention and calcium depletion are often marked. The precise mechanism by which the normal ratio of calcium to phosphorus is reëstablished is a matter of dispute. Albright and Ellsworth[11,12] believe that the primary effect of the parathyroid hormone is to increase the excretion of phosphorus in the urine, thus reducing the serum phosphorus, which results in a reciprocal rise in serum calcium. Objections to this view are presented by Thomson and Pugsley.[13] Whatever the mechanism may be, the observation that administration of parathyroid hormone is followed by reduction in the blood phosphate and increase in the blood calcium[14] provides the basis for the belief that secondary hyperfunction of the parathyroid glands may operate to prevent phosphate retention in nephritis. The fact is, however, that elevated blood phosphate and reduced blood calcium are very frequently observed in chronic nephritis, as, for example, in de Wesselow's series,[15] where 13 out of 69 patients had blood phosphate of over 10 mg. per 100 cc. This would seem to indicate that a compensatory mechanism, if it exists, frequently fails to prevent retention of phosphate in the blood. Phosphate retention was never observed in the patient we are reporting, hence this hypothetical stimulus to parathyroid hyperplasia was non-existent at the time of our observations. The fact that the blood calcium and phosphorus returned to their normal concentrations immediately following removal of the parathyroid adenoma and have remained there for the following 10 months, during which time the hypothetical stimulus provided by decreased renal function may be presumed to have continued, seems to us to render exceedingly remote the possibility of hyperparathyroidism secondary to nephritis in the present case.

Clinical data from the few reported cases analogous to this one are too dissimilar to lend themselves to close comparison. However, certain common features are worthy of mention in considering whether any basis exists for differentiation of this from other types of chronic renal disease. Many of the usual concomitants of chronic nephritis, *e. g.*, retinal exudates and hemorrhages, cardiac enlargement and peripheral edema, are absent or very inconspicuous in the reported cases of renal disease in hyperparathyroidism. A marked grade of renal insufficiency may exist, as in the present patient, without elevation of the blood pressure.[3,10,16–19] The urinary sediment is unusual in that the excretion of red cells, casts and albumin seems low in proportion to the degree of functional failure present. No one of these unusual features constitutes a trustworthy differential point, but together they result in a clinical picture sufficiently bizarre to suggest a search for other causes of renal failure.

A possible feature of differential value has been suggested by Albright and Bloomberg,[20] who have obtained from some of their patients granular casts which take up a specific stain for calcium and which dissolve when the urine becomes sufficiently acid. While not pathognomonic of hyperparathyroidism, their presence may suggest that possibility. No such casts were observed in our patient.

Polyuria, nocturia and polydipsia occur with striking frequency in hyperparathyroidism. They may be due to renal damage with consequent inability to excrete urine of high specific gravity.[2,10,19,21,22] However, the fact that these symptoms frequently disappear immediately after removal of a parathyroid tumor suggests that they do not necessarily indicate structural renal damage, but are rather the consequence of the excessive urinary excretion of calcium and phosphorus. When the inability to elaborate concentrated urine persists, as it has in our patient, for many months after correction of the disturbed mineral metabolism, it must be attributed to more permanent structural damage.

The data contained in Table 1 indicate that renal function in the patient we have described has remained practically stationary for almost a year after operation. There has been a slight increase in the figures for urea clearance and for rate of glomerular filtration, but the changes are not striking. The prolonged *P–R* interval observed in the electrocardiogram has persisted unchanged despite parathyroidectomy. *RS–T* interval deviations, present in another such patient,[23] were not seen in the present case. It is of interest that basal metabolic rate, observed to be low in the pre-operative period, spontaneously returned to normal after operation.

Summary. A patient is described who presented evidences of chronic renal disease with marked reduction in renal function. The classical picture of hyperparathyroidism was subsequently discovered. Diffuse calcification of the renal parenchyma, demon-

strated roentgenologically, is regarded as secondary to the disturbances in mineral metabolism, and probably responsible for the observed reduction in renal function. Removal of a parathyroid adenoma has given complete recovery from hyperparathyroidism, but has had in the one intervening year no striking effect upon the renal lesion.

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THE TREATMENT OF GONORRHEAL ARTHRITIS BY MEANS OF SYSTEMIC AND ADDITIONAL FOCAL HEATING.

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The Focal Nature of Gonorrheal Arthritis. The therapeutic problem of gonorrheal arthritis is intimately associated with the treatment of the etiologic focus in the genitourinary tract. Ever

since Fuller,[1] in 1905, stressed the importance of seminal vesiculitis in the male, the focal nature of this disease has been universally recognized. It is now generally conceded that in addition to the seminal vesicles, the prostate, posterior urethra and vas deferens play the most important rôles as the offending sites in the male.[2–6] In the female the cervix is regarded as the chief focus from whence gonococci may enter the blood stream and metastasize to the joints.[4,5,7–10]

The Use of Heat. Temperature elevation lends itself as a particularly rational and effective agent for the treatment of gonorrheal arthritis. As has been amply demonstrated *in vitro* the gonococcus can be destroyed at a level and duration of temperature within the limits of human tissue tolerance and safety.[11–18] The value of systemic elevations of temperature in gonorrheal arthritis has long been recognized, and the use of many agents other than physical ones have been widely advocated. Among these agents have been malaria,[19,20,21] gonorrheal vaccines,[6,22,23] typhoid vaccines,[6,22] as well as intramuscular milk, peptone, horse serum, and a host of other proteins.

Not only can effective heat dosage be applied with safety, but in gonorrheal arthritis heat can be utilized for many important therapeutic properties. Its direct destructive or attenuating influence on the gonococcus, if properly applied, can be exerted simultaneously in the blood stream, joints and in the areas of the original invasion. It is particularly important that the most vigorous action of heat can be exerted in the pelvic organs.[5,17,24,25] In addition to lethal or devitalizing action of heat directly on the gonococcus it has other indirect beneficial effects. As Mann,[24] Cumberbatch and Robinson,[5] Lees,[22] Hedrick[26] and others have pointed out, heat in the pelvis expedites drainage from the cervix, prostate and urethra, relieves pain, reduces swelling and assists in the vascularization of the part, increasing cell metabolism. It is important to remember that it can accomplish these therapeutic aims in the tissues of the joints as well. Certain beneficial systemic effects are also achieved with elevations of systemic temperature, such as, increased speed of circulation and increased number of white cells and phagocytosis in the blood stream.[27]

Combined Technique. The development of a technique to accomplish these therapeutic desiderata was based on a concept outlined by one of us 5 years ago.[28] The principle was to utilize combined systemic elevations of temperature with still higher pelvic heating. It was felt that a maximum effective dose of heat with a minimum of danger could be administered by this method. A technique which employed the short wave as the heating agent to achieve this dual heating effect was described in 1932.[29] A report presented in 1932[30] on the clinical application of the radiotherm technique in pelvic inflammatory disease also included its successful use in gonorrheal arthritis.

Systemic elevation of temperature by physical means without additional pelvic heating has been employed by others in the treatment of gonorrheal arthritis.[18,26] Still others, *i. e.*, Cumberbatch,[31] Nagelschmidt,[4] Mann,[24] van Puttee[25] described the application of only local pelvic diathermy for this condition.

The standardization and improvement on our original technique has depended on 4 factors: 1, The peak temperature necessary to kill all the known strains of gonococci; 2, duration of this peak; 3, penetration of the heat into the local regions within the pelvis; 4, anatomic considerations.

Carpenter, Boak, Warren and Wilson at Rochester found they could kill all strains of gonococci isolated from their patients in water baths at a temperature of 41.5° C. (106.7° F.) for 6 to 26 hours.[11,12] Utilizing this laboratory data they elevated and maintained the systemic temperature of each patient according to their findings. Boerner and Santos proved that the higher the temperature the less time was necessary to administer a thermolethal dose.[32] They found that gonococci could be destroyed at 44° C. (111.2° F.) in one-half the time required at 42° C. (105.8° F.). The difficulties in determining the thermal-death time of every strain in all patients under ordinary circumstances and in subjecting these patients to systemic treatments for more than 6 hours were obviously too great for universal practical application. We believed that it was more practical and effective to combine the systemic elevation of temperature (105° to 106° F.) with intensive heating of the pelvic foci (111° F.).

Methods. We have used various measures for the elevation of systemic temperature. These have included short-wave radiation (radiotherm), diathermy and photothermy. The most satisfactory technique we found to be as follows:

At the onset the patient was immersed in a water bath, the temperature of which was 100° to 102° F. The temperature of the water was then gradually elevated to 107° to 108° F. within about an hour. The rectal temperature was raised to about 105° F. within this time. As soon as this systemic temperature was achieved, the patient was transferred to a bed. This bed was covered with a hood containing a battery of 60-watt electric light bulbs. The photothermal effect of the lamps and the insulating properties of the hood made it a simple matter to maintain the systemic elevation of temperature. We considered it dangerous to attempt to maintain the temperature elevation in the hot bath.

To secure additional pelvic heating diathermy was administered. The active electrode was inserted in the rectum or vagina. The dispersive electrode was divided into 4 sections to avoid overheating of the skin and subcutaneous fat. In the female the rectal electrode was inserted and kept in place for 1½ hours. The current was gradually increased so that the hot-wire meter read 1500 to 2000 milliamperes. After this electrode was removed the vaginal electrode was inserted. The temperature of the tissue about the electrode was indicated by a thermometer within this device. This temperature was raised to 111° F. and then maintained for 3½ hours. The relationship between the temperature recorded by this

thermometer and that developed in the tissues of the pelvis was described.[33] The maintenance of these temperatures for 3½ hours did not usually cause any tissue injuries.[17] The current necessary for the development of this

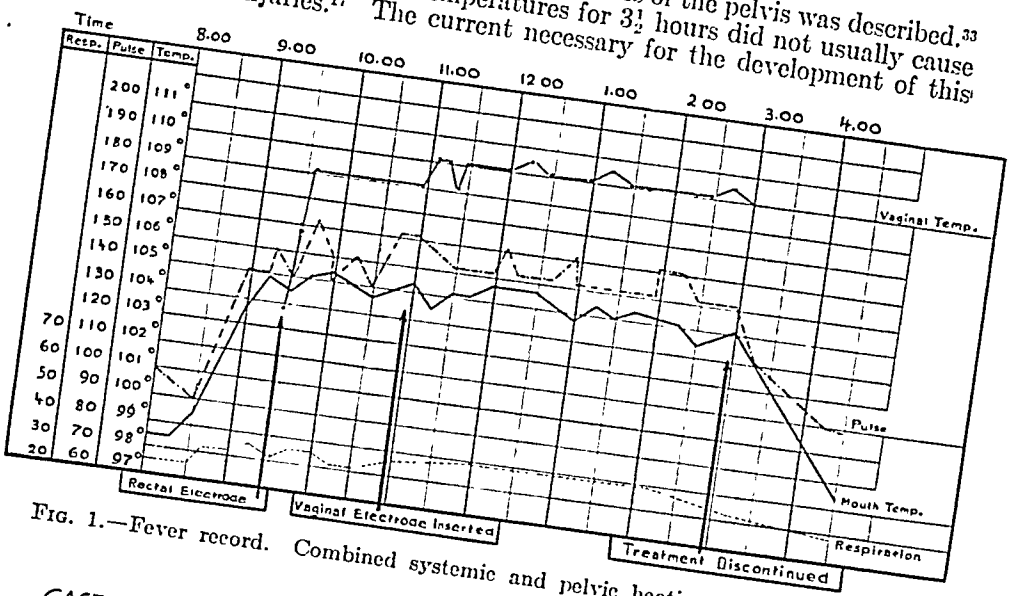


FIG. 1.—Fever record. Combined systemic and pelvic heating. Patient, N. F.

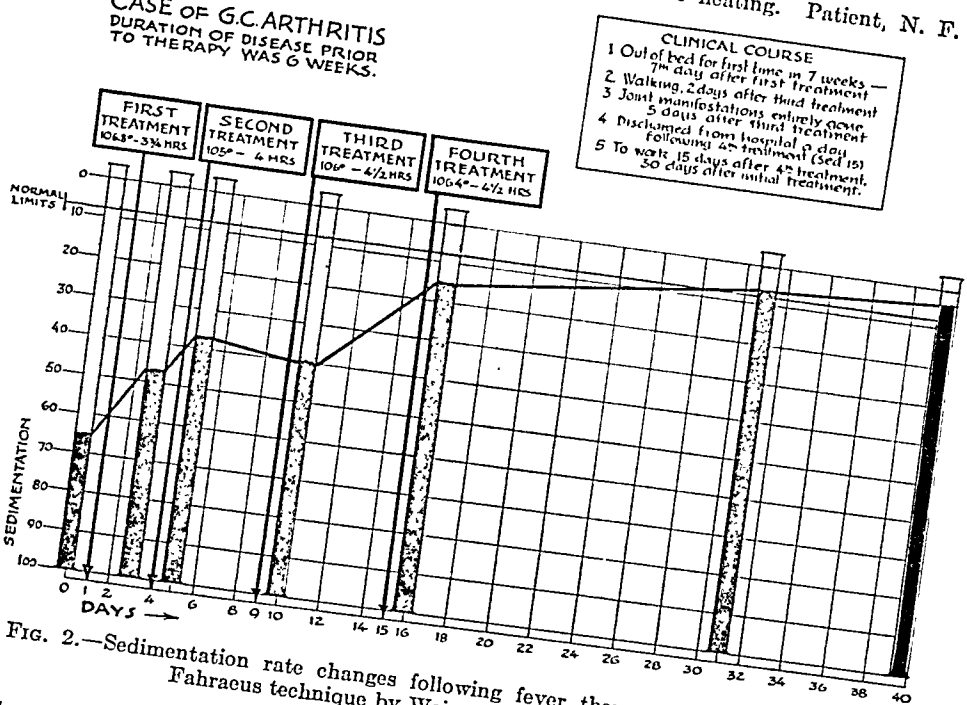


FIG. 2.—Sedimentation rate changes following fever therapy. (Modification of Fahraeus technique by Weiss—read in 45 minutes.)

temperature varied from 2000 to 3000 milliamperes. This gave effective penetration of heat into the pelvic organs in the female.[17,33] Thus a temperature of about 111° F. was maintained in the female pelvis for at least 3½ hours.

The anatomic structure in the male did not present a cavity into which a large metal electrode could be inserted so that it lay in close proximity to the genital foci of infection. It was found necessary to utilize the rectum for this purpose. To prevent overheating of the rectal mucosa while attempting to achieve a maximum heat influence upon the posterior urethra, prostate and seminal vesicles, the metal electrode was water-cooled. By this means the involved tissues at a distance were heated conversively while the rectal mucosa was protected by the conductive influence of the water. This cooling arrangement was necessary because the rectal electrode in the male was kept in place for 3 to 4 hours. The milliamperage used was 1500 to 2000.

By controlling the lights in the hood and the amount of diathermy current the degree of systemic temperature could be varied. The mouth temperature which usually was 0.7° F. below the rectal temperature, was used as the index of systemic elevation.[27] The systemic elevation was maintained for 5 to 6 hours at about 105.5° F. by mouth.

Adequate supervision and care were necessary to avoid serious sequelæ. The patients were made comfortable by the use of sedatives. Water was given as desired. The preparation of the patient consisted of an enema. A light breakfast was permitted. Females were not treated for 3 days before, during, or 3 days after the menses.

Clinical Data. *Number of Treatments.* A group of 16 cases of gonorrheal arthritis, 8 male and 8 female, who receive this combined treatment are included in this study. The average number of treatments per case decreased as the technique was improved. From the very onset the female cases required fewer treatments than the male because effective pelvic heating was more easily achieved in the former. The 8 women received an average of 2.1 treatments per case; the 8 men got an average of 3.5 treatments per case. The largest number of treatments given to any one case was 6. When the radiotherm was used, the 4 male and 3 female cases treated with it averaged 3.5 treatments per case. Later when diathermy was substituted for radiothermy, the technique became more successful. The 6 cases, 4 men and 2 women, treated with this improved procedure had an average of 2.83 treatments per case. After the bath technique was introduced, 3 females were treated. In each of these cases only one treatment was found necessary for their arthritic complications. Recently with the use of the water-cooled rectal electrode in the male 1 treatment sufficed to clear up the urine in the second glass of the two-glass test.

Interval Between Treatments. The shortest interval between treatments was 2 days; the longest 13 days. The 17 treatments administered to the 8 females were spaced at average intervals of 2.7 days apart; the 28 treatments given the 8 males were at an average of 3.22 days apart.

Analysis of Clinical Material. Each of the cases included in the series received hyperpyrexia with pelvic heating only after he or she had been through the gamut of other forms of therapy. All but 2 came with active gonorrheal lesions and painfully swollen joints in various stages of immobilization. In addition the patients in

this series had been invalided in bed from 2 weeks to 3 years. All but 2 cases were acutely ill just before treatment with active systemic reactions including fever at the time of the first treatment. The 2 exceptions who had no evident active gonorrheal foci, however, had permanent bony synostosis and other chronic joint Roentgen ray changes with only moderate pains and little swelling.

Treatments before Hyperpyrexia. The variety of treatments used in the past was reflected in the wide range of therapy to which these 16 cases had been subjected before getting this combined procedure. The variety significantly indicated the inadequacy of any of the previous procedures in these cases. None had received any permanent relief and two had permanent pathologic changes in their joints. The attempts to eradicate focal lesions included the use of such gonococcides as silver nitrate, acriflavin, protargol, and mercurochrome as well as rectal and vaginal diathermy. All females had cervicitis; 6 had urethritis; 3, Skene's ducts involvements; 2, adnexal complications. Among the 6 males with active foci; all had urethritis and prostatitis; 3 had epididymitis; and 2 had vesiculitis.

Previous attempts to create favorable systemic reactions were unsuccessful; 14 of the cases had received intravenous chemotherapy (mercurochrome and colloidal sulphur), foreign proteins (typhoid vaccine, milk and whole blood), as well as various types of autogenous and stock gonococcal vaccines (9 cases). This type of treatment depended upon protein shock and systemic temperature elevation for success.[6,19–23] The temperature and systemic reactions to this type of therapy could not be carefully gauged and controlled and were ineffectual.[3]

All local joint therapy also failed to give permanent results in these 16 cases. The procedures which had been tried either alone or in combination before included the following: tapping, immobilization, traction, diathermy, baking, massage, wet dressings, early mobilization and local use of Roentgen ray. All came for the combined treatment with varying degrees of joint pains, swelling, tenderness and immobilization.

Average Age—Duration—Past Histories. The age of these patients had no influence on the course of their disease nor on the type or number of treatments. Although no patient with gonorrheal arthritis had been refused treatment because of age or any degenerative changes, patients with marked arteriosclerosis, aneurysm, or coronary artery disease were refused similar treatment for other conditions such as lues. The average age of the group was 31.2 years. The oldest female was 44 and the youngest 27 years; the oldest male was 38 and the youngest 23 years.

The average duration of the gonorrhea in the 14 with active foci was 12.8 weeks; the longest duration was 28 weeks and the shortest 4 weeks. The average duration of the arthritic manifes-

tations in the active group was 10.2 weeks; the longest period of arthritis was 25 weeks, the shortest was 3 weeks. The importance of early treatment will be discussed later.

Three of the 8 male cases had definite previous gonorrheal histories. One case gave a 7-year history of chronic gonorrheal prostatitis before the acute flare-up that led to his arthritis. There was no previous history of gonorrhea in any of the female cases.

Response to Treatment. The response of the systemic and joint manifestations of all the cases to treatment was satisfactory and in some cases dramatic. Temperatures subsided, malaise and chills and sweats disappeared, red cell sedimentation rates showed return toward normal and the patients were able to get out of bed within 4 to 12 days after the complete course of their treatments. In the 4 cases which had rashes, 1 of which was proven by biopsy to be a gonorrheal paraketosis, the skin lesions disappeared within a week after this procedure. The joint symptoms and signs invariably subsided with remarkable uniformity. In every instance there was a definite change for the better. There was a rapid subsidence of pain, diminution of swelling and increased mobility.

Good functional results were obtained in all but the 2 cases that came with evidence of bony fusion as indicated by Roentgen ray. Of the other 14, 13 were completely freed of their pain and achieved perfect function. The remaining case was that of a female who when seen 2 months after her course of 3 treatments still showed about 50% of limitation of motion in the wrist and fingers. This was steadily improving under the local after treatment.

Need for After Treatment to the Joints. Although combined use of hyperpyrexia and pelvic heating can promptly stop the ravages of the gonococci in the joints, this procedure cannot be expected to restore distorted anatomy with equal rapidity. The 2 cases of bony ankylosis required arthroplasty. In the other cases where the soft tissues were the seat of inflammatory reactions, the muscles and tendons atrophied and bones rarefied by disuse, supplementary measures for complete restoration were used. Massage, local photothermy, diathermy, local short wave and graduated passive and active exercises, especially under hot water, were of great value. The earlier the patients were treated in the course of their disease, the less did they require after treatment. Three patients who came within 6 weeks after onset required no after treatment. Occasionally complete restoration required as much as 6 to 8 months. This was especially true of cases who came late in their illness.

Eradication of Foci. Among the females the gonorrheal foci were more easily eradicated than among the males. The effectiveness of this method of treatment in the female was described.[17]

In the males definite evidence of the effect of this treatment on the local gonorrhea was obvious. The discharge decreased in amount. The second glass of the two-glass test usually became

clear indicating the subsidence of the infection in the posterior urethra. The anterior urethra did not clear up as quickly because its temperature could not be elevated to as high a level. In order to eradicate the organisms which still remained, the usual anterior urethral injections of gonococcidal solutions were employed, such as, mercurochrome, acriflavin and the silver salts.

The course of each case before and after treatment was followed by a gynecologist or an urologist especially trained in gonorrhea. The smears were studied by two and sometimes three individuals with extensive experience in gonorrhea. No case was considered free of gonococci until a thorough follow-up for periods ranging from 3 to 6 months had failed to reveal any evidence of the disease. Some of the cases were followed for more than 1½ years so that conclusive proof against recurrence of hidden foci could be obtained.

Sedimentation Rate and Clinical Progress. In the evaluation of clinical progress, the red cell sedimentation rate was the most satisfactory and practical of all the objective tests. The Weiss modification of the Fahraeus technique was used because of its simplicity.[34] The drop in sedimentation rate closely paralleled clinical improvement of the joints. Among the 16 cases in this series the return to normal often did not occur until after 6 weeks. This delay in return to normal probably was due to the gradual absorption of residual débris and the slow healing of the previously inflamed tissues.

Case Reports. To illustrate the clinical course of gonorrheal arthritis treated by this method, we cite a typical male and a typical female case:

CASE 1.—B. S., male, aged 34, single, steamfitter.

Previous History. Two previous attacks of gonorrhea, 9 and 4 years before. During second attack, had epididymitis and buboes. Made an apparent recovery after 7 months of treatment.

Course Before Treatment. Date of exposure was January 15, 1934. One week later, 26 weeks before treatment, he developed a urethritis which soon involved the posterior urethra, prostate and epididymus. A week after the onset of the gonorrhea, the joint manifestations began with chills, fever and pains in the right knee. He was sent to a hospital where right shoulder and left hip also became involved. Each of these joints had some degree of pain, swelling, tenderness and immobility. He was completely bedridden for 1 month and during this time he received a course of gonococcal vaccine and hydrotherapy as well as local treatments for the urethra and prostate. He was discharged from this institution as "improved." Because of the persistence of his discharge as well as joint symptoms, he went to the out-patient department of another institution where his knee was tapped, intramuscular injections of milk were administered and massage and diathermy to the joints were given. Although he was able to attend this clinic once a week for several months, he gradually became worse, so that just before coming to us on June 23, 1934, he was unable to bend over and tie his shoelaces and unable to get out of bed without assistance.

An examination 2 days before treatment revealed the following: Temperature, rectally, 100.2° F.; profuse purulent urethral discharge; numerous

gonococci in urethral and prostatic smears; prostate large and boggy; right epididymus enlarged, painful and tender; the left shoulder moderately painful with a periarticular swelling and motion limited to 50%; right knee and ankle markedly swollen, red, painful and tender; required crutches in walking; unable to bend knee more than 15%. In addition to the positive smears, he had a positive complement fixation; both glasses of the two-glass test were cloudy; sedimentation rate of 39 mm. A Roentgen ray examination at this time showed osteoporosis of the bones entering into the formation of the right shoulder and right knee.

Treatment. He received 3 treatments. Each time an oral temperature about 105° F. was maintained for more than 5 hours. Rectal diathermy was used for 3½ hours.

Course After Treatment. After the first treatment he could bend over and get in and out of bed with no difficulty, raise his left arm to within 75% of the normal range. Pain and swelling in the joints diminished. Sedimentation rate fell to 26 mm. Discharge from urethra became less profuse. Two-glass test results were: first glass hazy; second glass entirely clear with few shreds. Complement fixation remained positive. Received local instillations of 0.5% protargol twice a day and diathermy to the ankle.

After the second treatment he had stiffness of the right knee, but it was much less than before, pains in the left shoulder, right knee and ankle were almost entirely gone; could tie his own shoelaces without difficulty and could raise shoulder to within 85% of the normal range. He walked with a cane. His discharge had further decreased, although the smears remained positive; sedimentation rate fell to 18 mm. The local instillations and diathermy to the ankle were continued.

Two days after the third treatment there was no stiffness in the ankle or knee; no pain in the shoulder which still had a 5% limitation of motion on direct extension upward. Although urethral discharge was hardly noticeable, his smears remained positive. The pains in the ankles and knees as well as the swelling of all the joints disappeared. Cane was discarded. The two-glass test results were: first glass, still slightly hazy; the second contained only a few shreds. His epididymitis had disappeared. The complement fixation remained positive. Progressive exercises were used to overcome a slight residual stiffness of the joints in the morning and the 5% limitation of motion of the shoulder joint. This cleared up in a few weeks.

Protargol instillations were continued for about 3 weeks after hyperpyrexia. After this the smears became negative, discharges entirely disappeared, sedimentation rate came down to 6 mm. and complement fixation was reported as negative. Fifteen subsequent smears were all negative. Three subsequent sedimentation tests were all normal. The complement-fixation tests remained negative.

Eight months after his course of treatment, at a final check-up, there was complete restoration of joint function and no recurrence of any pains. Patient was seeking reëmployment. Provocative smears after alcohol and chemical irritation remained negative. There was no laboratory or clinical manifestation of gonorrhea. Sedimentation rate was 4 mm. Roentgen rays were normal.

Case 2.—C. L., female, aged 33, married, housewife.

Previous History. Irrelevant.

Course Before Treatment. Developed urinary symptoms with urethral and vaginal discharge within a week after exposure, November, 1933. A few days later, following a chill, she developed joint symptoms and became bedridden for 5 weeks. The following joints were involved in chronologic order: right heel, right hand, right shoulder, left shoulder, left hand

and left ankle. She was bedridden and hospitalized. Despite 7 intramuscular injections of milk and the use of gonococcal vaccine, as well as several applications of silver nitrate to the cervix, she continued to get worse.

She was then transferred to our institution. At that time she was acutely ill with a rectal temperature of 103° F. She had profuse urethral and cervical discharges which contined many gonococci. Her joint manifestations consisted of: pain, swelling and a 40% immobility of the left knee; and pain with a 10% immobility of the left shoulder. There was complete immobility of the left ankle with marked pain, swelling and exquisite tenderness, associated with footdrop. Complement fixation was positive and sedimentation rate was 36 mm. Roentgen ray showed no bony changes.

Treatments. She received 3 treatments. In each instance the systemic temperature was maintained above 105° F. by mouth for more than 4½ hours. The vaginal temperature was maintained between 109° F. and 111.2° F. for more than 3½ hours. Rectal diathermy for 1½ hours preceded vaginal diathermy.

Course After Treatment. After first treatment the joint pain and redness began to diminish as did urethral discharge. There was a 10% increase of motion of the knee and restoration of complete motion of the shoulder. The ankle remained immobile. There was little change in sedimentation rate.

Following second treatment the cervical smear remained positive. There was some residual stiffness, pain and tenderness of the left knee. The left ankle was still immobile but the pain and swelling of this joint were also almost entirely gone. There was a marked subjective improvement after this treatment. For the first time since her stay in the hospital, she moved freely in bed without pain and slept well.

Twenty-four hours after last treatment all signs and symptoms in the left shoulder disappeared as did the pain, redness and tenderness of the left knee. The motion of the left knee was within 60% of normal. There was a barely perceptible swelling about the left ankle and a moderate amount of bluish discolorization. Passive motion beyond 20% of normal range still gave pain in this joint. Both cervical and urethral smears became negative and the sedimentation rate fell to 12 mm.

Five days after her last treatment she was able to get out of bed for the first time. She used crutches for 1 week and then used a cane for support. The footdrop persisted for several weeks as did the periarticular thickening about the ankle. Massage, diathermy, radiant heat and light and graduated exercises had to be carried out for 3 months before she could discard the cane and walk without a limp. At this time she was able to wear high heels and carry on her entire schedule of housework without difficulty.

More than 12 urethral and cervical smears over a period of 6 months remained negative. Complement fixation became negative 7 weeks after treatment and remained negative. The sedimentation rate became normal 8 weeks after treatment and remained normal. A final check-up 9 months after treatment revealed no recurrence of joint or genitourinary signs or symptoms.

Summary. A method is described for the treatment of gonorrheal arthritis by means of systemic and additional pelvic heating. This method in addition to local joint and genitourinary after treatment was successful in causing the eradication of the causative organism and the rapid disappearance of pain, where they existed, in all of

the 16 cases treated. Restoration of function with complete joint mobility occurred in 13 cases, partial restoration in 1 and very little increased mobility in 2—both of which had bony ankylosis when they presented themselves for treatment. All of these cases had been treated without lasting improvement by various methods advised at present. Our experience leads us to believe that hyperpyrexia, applied with the technique described, is the most effective means available for the treatment of gonorrheal arthritis. It should be administered as early as possible in order to avoid permanent pathologic changes and deformities.

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TOTAL BLOOD FAT DETERMINATION AS AN INDEX OF THYROID FUNCTION.*

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The diagnosis of thyroid disease is still not so easily accomplished as is indicated by the reading of standard texts. In many instances of indefinite symptomatology, considered to be attributed to dysfunction of the thyroid gland, determination of the basal metabolic rate has been invaluable. There are, however, several rather marked limitations on the use of this procedure in actual practice: the patient may be so mentally retarded or emotionally unstable as to be incapable of giving the requisite coöperation, or he may be so apprehensive as to consume much larger amounts of oxygen than really demanded by the tissue with an erroneously high reading, or he may be a child who cannot be satisfactorily inducted into the ritual attached to the performance. Not infrequently, such patients are precisely those of whom knowledge of the basal metabolic rate is needed for an estimation of the thyroid function. Numerous tests have been tried to avoid the large subjective element inherent in all studies of basal metabolism but none has succeeded so well as has the determination of the blood cholesterol.

It has long been known that there exists some relationship between the level of the cholesterol in the blood and the deviation from normal of thyroid function. Hurxthal[1] found that in exophthalmic goiter, recurrent hyperthyroidism and adenoma of the thyroid associated with hyperfunction of the gland there is a depression of plasma cholesterol, the lowest values being obtained in patients in or near a crisis. In adenomata of the thyroid not associated with evidences of hyperthyroidism there was a normal blood cholesterol. In myxedema and chronic thyroiditis, there was always an elevated cholesterol.

Bronstein[2] commented on the common dissatisfaction with basal metabolic rate determinations in cretins. In a group of

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thyroid deficient children whom he studied, there was an elevated plasma cholesterol. He withheld thyroid extract from known cretins and observed that as they became clinically worse, there was a concomitant rise of cholesterol; when he resumed feeding of thyroid extract and the children improved, there was an associated decrease of the plasma cholesterol. He noted that this hypercholesterolemia was not affected by administration of insulin, thereby differing from the hypercholesterolemia of diabetes mellitus.

Simonds and Helpher[3] rendered dogs hyperthyroid by feeding large amounts of desiccated thyroid and then studied their tolerance to olive oil administered enterally. Whereas their normal controls had increased blood lipoids after ingesting these fats, the hyperthyroid dogs had a much smaller increase of the blood fats after the fatty meal, while their fasting blood fats were lower than the fasting blood fat of the normal control.

Hurxthal[4,5,6] later demonstrated that cholesterol determinations were of definite diagnostic value in considering abnormalities of the thyroid gland. Usually, the test was of greater usefulness when hypothyroidism was being suspected. In this condition, the plasma cholesterol tended to deviate from the normal four times as much as did the basal metabolic rate, whereas in hyperthyroidism the basal metabolic rate and the plasma cholesterol tended to deviate from the normal about the same amount. In myxedema, the values were always increased and subsequently lowered when thyroid extract was administered. In hyperthyroidism, either of the exophthalmic type or of the adenomatous type, the values were generally lower than normal and tended to return to normal on the administration of Lugol's solution or after subtotal thyroidectomy. Gilligan *et al.*[7] showed that in the myxedema induced by the total thyroidectomy for cardiac disease the plasma cholesterol was a more delicate and reliable indicator of the state of metabolism than was the basal metabolic rate. Other observers have demonstrated that there occur clinically states wherein the basal metabolic rate may be 20 to 30% below normal and yet the individuals show no evidences of myxedema or of other manifestations of lessened thyroid function. In such conditions the plasma cholesterol is normal. Whenever the plasma cholesterol rises above normal (unless there is diabetes mellitus, arteriosclerosis, nephrosis or obstruction of the common bile duct), the individual is suffering from decreased thyroid function.

From the above it is evident that study of the cholesterol level may be utilized as a means of determining the presence or the extent of abnormality of thyroid function if the cited conditions are borne in mind. Wherever applicable, the study of blood cholesterol furnished valuable information.

Unfortunately, accurate determinations of blood cholesterol are difficult and time consuming, involving detailed and elaborate

technique, and requiring a trained technical staff. Rückert[8] has shown that study of the total lipids of the blood is very often informative where plasma cholesterol determinations are not available. The technique is much simpler and shorter, and is less subject to experimental error. Collins,[9] following Rückert's technique, and Herrmann,[10] with minor modifications, have shown by comparative determinations that the level of the total blood fats as obtained by the simple lipocrit method parallels that of the cholesterol.

In a series of 35 clinic and house patients (Medical Service, Touro Infirmary), we have attempted a follow-up study of total blood fat levels and have interpreted them in the light of clinical symptoms, and other laboratory diagnostic determinations including basal metabolism. The specimens for total lipoids were taken at 14-hour fasting levels. Whenever possible, basal metabolic rates were done at about the same date that the lipoid studies were carried out. The technique of the lipocrit method employed is essentially that of Rückert as described in his original article. We have regarded values of 500 to 700 mg. per 100 cc. of blood as normal, but have not accepted any value as definitely depressed unless below 400. In the following table we have summarized our findings.

TABLE 1. TOTAL LIPOIDS IN 35 CASES

Case No. Patient.	Age. Sex.	Date.	B. M. R.	Total fat.	Remarks.
1. H. B.	40 F.	11/21/34	+17%	687	Clinical evidence of hyperthyroidism including a palpable gland, familial tendency. Responded to Lugol's solution given after second blood fat determination. Coöperation for B. M. R. very poor.
		12/ 7/34	+44%	416	
		4/ 1/35	—	592	
		4/15/35	—	541	
		5/15/35	—	540	
2. H. R.	22 F.	12/21/34	−6%	512	Colloid goiter. Both B. M. R. and blood fats within normal limits.
3. F. B.	52 M.	11/ 5/34	+31%		Vasomotor instability. Anxiety state. Illustrates fallacy of relying on the B. M. R. determination in unstable patient.
		11/19/34	+21%	728	
		11/23/34	−12%		
		1/28/35	−6%	656	
		3/18/35	—	864	
		4/12/35	—	812	
4. Z. D.	28 F.	4/ 9/34	+30%	..	Toxic adenoma. Lugol's solution beginning 4/15/34 for 6 wks. Subtotal thyroidectomy 6/13/34. Postoperative blood fat determinations confirm clinical impression of normal thyroid function.
		5/ 4/34	+14%		
		6/ 6/34	+8%		
		8/ 1/34	−15%		
		12/21/34	0	688	
		1/30/35	0	536	
		3/29/35	—	576	
		5/20/35	—	560	
5. B. L.	18 F.	11/14/34	−6%	472	Lorrain Levi type of dyspituitarism. Positive response to antuitrin in terms of skeletal growth and development of sex function. Persistent obscure low grade fever may account for the subnormal blood fats.
		3/22/35	—	336	
6. S. M.	17 M.	11/16/34	−15%	471	Problem of both tuberculosis and thyrotoxicosis. Patient symptomless. Blood fat not sufficiently depressed for thyrotoxicosis.
		3/25/35	—	460	
7. L. D.	44 F.	9/21/34	+28%	..	Menopausal syndrome. Pott's disease (? activity). Variable B. M. R. and consistent blood fats in absence of definite thyroid disease; also illustrates difficulty in determining B. M. R. when body surface cannot be calculated because of kyphosis.
		12/20/34	—	568	
		2/ 8/35	−22%		
		5/ 3/35	+20%	520	

TABLE 1. TOTAL LIPOIDS IT 35 CASES—*Continued.*

Case No. Patient.	Age. Sex.	Date.	B. M. R.	Total fat.	Remarks.
8. G. W.	45 F.	10/10/34	+30%	..	Secondary lesions in 1924, followed by inadequate treatment. Hysterectomy, Sept., 1933. Lugol's sol. 10 min. t.i.d. from Oct. to Feb. Fall in B. M. R. with rise in blood fats during administration of iodin (discontinued 2/11/35).
		11/ 9/34	+14%	680	
		2/ 1/35	+19%		
		2/11/35	—	832	
		5/15/35	—	432	
9. A. R.	32 F.	2/14/35	+8%	632	[illegible] thyroidism as evidenced by two normal blood fats.
		4/10/35	—	520	
10. E. C.	62 F.	9/15/33	+72%	..	Thyrotoxicosis with auricular fibrillation, Sept., 1933. Thyroidectomy, 10/16/33. All symptoms subsided postoperatively. Marked gain in weight, 132 to 191 pounds.
		9/25/33	+62%		
		12/13/33	−3%		
		4/ 2/34	+8%		
		1/ 7/35	—	552	
11. O. L.	38 F.	1/ 2/34	0	..	Hypertension with vasomotor disturbance, psychoneurosis. The recent B. M. R. and fat determinations show thyroid hypofunction; the symptoms suggested thyroid hyperfunction.
		3/ 4/34	+27%		
		1/28/35	−18%	872	
		4/ 8/35	..	728	
12. V. E.	15 F	1/30/35	+14%	..	Loss of weight, repeated colds, low grade fever, nervousness. Tuberculosis or hyperthyroidism? Low blood fat is probably result of sinus infection although hyperthyroidism is possible.
		2/ 4/35	—	344	
		5/13/35	—	344	
13. M. S	42 F.	12/20/33	+21%	..	Normal blood fat in a menopausal syndrome. Bilateral salpingo-oöphorectomy, 6/20/33, then pronounced menopausal symptoms. Developed mild hypertension with no changes in visual fields or eye grounds. Sella turcica enlarged. Increased dextrose tolerance. Impression: post-castration pituitary dysfunction, menopausal syndrome.
		3/ 9/34	+27%		
		1/30/35	+2%	672	
		4/ 5/35	—	640	
14. F. C.	18 F.	6/ 1/34	−3%	.	Lorrain Levi type of hypopituitarism. Grew 1¾ in. with antuitrin therapy. Very little subsequent growth with antuitrin or thyroid extract. Normal blood fat level.
		1/ 3/35	—	488	
		4/ 8/35	—	520	
15. S. B.	32 F.	1/30/35	−12%	728	Unstable colon, malnutrition, depressed thyroid function. Marked improvement with diet, belladonna and thyroid extract.
		4/ 5/35	—	696	
		5/13/35	—	680	
16. E. T.	20 F.	9/25/34	+11%	.	Nervousness, cough, afternoon fever, fine tremor, palpable thyroid. Tuberculin xx. Roentgen ray of chest repeatedly negative. Lugol's solution, drops 10, t.i.d. from 3/12/35 to 4/1/35. Early tuberculosis, hyperthyroidism or psychoneurosis? The low fat showing no rise following iodin is not caused by thyrotoxicosis, may be due to tonsillar infection.
		2/25/35	—	432	
		3/20/35	—	384	
		4/ 1/35	—	388	
17. C. P.	46 F.	4/ 1/35		342	Loss of weight, increased appetite, nervousness. Exophthalmos, hypertension. Lugol's solution, drops 10, t.i.d. started 4/4/35, with a slight response.
		4/10/35	..	392	
		4/26/35	..	440	
18. M. B.	24 F.	2/ 1/35	+13%	..	Marked postpartum gain in weight in woman who had periodic premenstrual diarrhea of 4 mos.' duration. Uterine inertia during labor. The single B. M. R. determination is confirmed by the 2 normal blood fat determinations.
		3/ 8/35	—	496	
		3/22/35	—	376	
		5/13/35	—	592	
19. V. M.	25 F.	2/21/35	—	432	Dizziness, tachycardia, loss of weight, palpable thyroid. Lugol's solution begun 3/7/35, with negative reaction.
		3/ 4/35	+3%		
		5/ 6/35	—	424	
20. L. B.	57 F.	2/25/35	—	1,240	Suggestive thyrotoxicosis in 1907. No laboratory studies available. Diagnosed hypothyroid in 1922; improved with thyroid feeding. Discontinued in 1924. Symptoms of weakness, fatigability and substernal pain. B.P. 187/110. Ekg. shows coronary sclerosis. Thyroid medication, 3/20/35. Caused marked blood fat response.
		3/11/35	−26%		
		3/20/35	—	1,060	
		4/17/35	—	560	
		4/21/35	—		

TABLE 1. TOTAL LIPOIDS IN 35 CASES—*Continued.*

Case No. Patient.	Age. Sex.	Date.	B. M. R.	Total fat.	Remarks.
21. A. D.	45 F.	7/20/34	+7%	..	Rheumatic heart disease with congestive failure. Total ablation of thyroid, 7/2/34. Postoperative myxedema was associated with definite increase of blood fats above normal at a time when B. M. R. was only slightly depressed.
		7/21/34	−5%		
		11/ 4/34	−2%		
		11/21/34	−	792	
		12/ 2/34	−2%		
		3/18/35	.	848	
		4/25/35		832	
22. E. G.	42 F.	2/ 1/35	+37%		Hypertensive heart disease. Healed Pott's disease. Hyperthyroidism with palpitation, loss of weight, tremor. Subjectively improved following bed rest, begun 2/2/35, iodin and sedation. Blood fat level at low normal on 2 occasions, *i. e.*, is not always definitely lowered in mild hyperthyroidism.
		2/ 9/35	+21%	462	
		2/19/35	11%	520	
		2/19/35	+37%	472	
23. R. A.	27 F.	3/15/35	−	592	Nervousness, palpitation, tremor, nodular goiter. Diagnosis non-toxic adenoma. Shows 2 normal blood fats in spite of some variation in the B. M. R.
		3/30/35	−23%		
		4/ 3/35	−7%	568	
24. J. E.	30 F.	11/12/34	+26%	.	Hyperthyroidism with a diffusely enlarged gland. Lugol's begun 11/14/34 and stopped 12/5/34. Apparent response to iodin as judged by B. M. R. Present clinical picture of non-toxic goiter is confirmed by normal fat.
		12/ 7/34	−7%		
		3/ 9/35	+2%		
		3/ 3/35	−	544	
		3/13/35	−	544	
25. C. R.	22 F.	2/22/35	−11%	504	Pregnant 3 mos. when first seen, 2/19/35. Tachycardia, dyspnea. Palpable thyroid. Physical signs and history suggest rheumatic heart disease. Tests with Lugol's during which time the B. M. R. rose from 13 to 27%, and the blood fats remained practically stationary illustrate fallacy of relying entirely on rising B. M. R. in pregnancy. Blood fat determination assisted materially in differentiating between hyperthyroidism and rheumatic cardiac disease.
		3/ 4/35	+13%	656	
		3/27/35	+24%	592	
26. R. A.	49 F.	1/25/35	+10%	616	Menopausal syndrome with questionable hyperthyroid function. Negative response to iodin in that blood fat fell during the administration of Lugol's solution.
		5/ 6/35	−	432	
27. M. F.	15 F.	9/ 7/34	−9%	..	Colloid goiter. No abnormal findings except enlarged thyroid, which first appeared with beginning menstruation.
		11/ 3/34	0		
		4/ 1/35	−13%	412	
28. S. K.	45 F.	9/29/34	+25%	...	Menopausal syndrome.
		11/26/34	..	558	
		1/22/34	+9%	632	
		4/15/35	..	552	
29. I. F.	43 F.	2/11/35	−12%	592	Subtotal thyroidectomy in 1927. In 1929 recurrence of typical hyperthyroid symptom complex. Second thyroidectomy. Postoperative hypoparathyroidism with symptoms of tetany and convulsions with intermittent treatment from 1929–1935. Marked improvement under calcium and parathormone. 3/15/35 ankle edema, Ekg. evidence of myxedema heart. Thyroid, gr. ½, b. i. d.
		3/20/35	−19%	712	
		3/29/35	−7%	640	
30. K. K.	52 F.	5/ 8/35	+39%	432	Nervousness, tremor, increased appetite, intolerance to [illegible]. Surgical menopau[illegible] solution, min. 20. [illegible] Positive response [illegible] hyperactive thyroid.
		5/13/35	+33%	424	
		5/22/35	+16%	504	
31. V. B.	24 F.	11/ 9/34	+8%	..	Nervousness, loss of weight, diarrhea (over period of 11 yrs.). Treated for "goiter" with iodin at intervals. The 2 normal blood fats following iodin would indicate normal thyroid function.
		12/14/34	−24%	404	
		3/27/35	−	595	
		5/15/35	−	560	
32. H. B.	35 M.	4/17/35	+7%	480	Nervousness, loss of weight, tachycardia, fatigability. Thyroid diffusely enlarged, soft. Lugol's solution, min. 10, t. i. d. from 5/6/35 to 5/16/35. Even though this is a suggestive response to iodin, the relatively slight rise was considered insignificant. Diagnosis, anxiety neurosis.
		5/ 1/35	+17%	472	
		5/ 6/35	+10%	532	
		5/10/35	−	560	

TABLE 1. TOTAL LIPOIDS IN 35 CASES—*Continued*:

Case No. Patient.	Age. Sex.	Date.	B. M. R.	Total fat.	Remarks.
33. M. A. . . .	67	5/ 6/35 5/ 8/35	−10% −2%	592 640	Drowsiness, fatigability, dry skin, coarse hair, spade hand. Diagnosis, normal thyroid function in spite of clinical picture because of the normal blood fat and B. M. R. determination.
34. P. T. . . .	34 F.	5/31/35	+23%	512	Nodular goiter since puberty with enlarged gland during first pregnancy 3½ yrs. ago. Patient is now 5 mos. pregnant and presents symptoms suggesting toxicity for first time.
35. L. G. . . .	34 F.	5/29/35	+30%	768	Diabetes for 7 yrs. Moderate fullness of thyroid noted 4 yrs. ago. Diagnosis of toxic adenoma made 2 yrs. ago, B. M. R. then +37%. During past 6 mos. diabetic status has become most unstable with recurrence of symptoms of hyperthyroidism and mild acidosis. The blood lipoid level cannot be evaluated until the acidosis factor is eliminated.

Summary. We do not suggest that determinations of the total lipoids should supplant any method used at the present for the study of metabolic disorders; rather it is offered as a valuable addition. We feel that it will afford as much information as will determinations of plasma cholesterol in that it is consistently elevated above the normal 700 mg. per 100 cc. in hypofunction of thyroid and generally below 400 mg. in hyperthyroidism. In mild cases of hyperfunction it is apt to be between 400 and 500 mg., at which level the diagnostic import is questionable. It is not materially affected by any other endocrine gland disorders, except diabetes, as long as the thyroid is not demonstrably involved.

It is exceptionally of value in those patients for whom the determination of the basal metabolic rate is not feasible.

The depression of the basal metabolic rate following administration of iodin, such as Means[11] has shown to be a routine diagnostic test for hyperthyroidism, is paralleled by the increase of total lipoids. Conversely, its failure in response to iodin is regarded as of significant negative value.

We wish to express our appreciation to Dr. I. I. Lemann, Professor of Clinical Medicine, for his advice and coöperation and the permission to use his patients for this study; to Dr. A. B. Pitkin for his coöperation in the metabolic determinations, and to Miss Baumgartner of the Touro Infirmary Social Service Department in the follow-up studies.

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THE EFFECT OF THERAPY ON NERVE DEGENERATION IN PERNICIOUS ANEMIA.

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The eminently satisfactory results which attend the treatment of the anemia of pernicious anemia by adequate therapy, whether liver, its extracts, or their equivalent are universally accepted. More controversial, however, is the effect of such treatment upon the subacute combined degeneration which sooner or later makes its appearance in this disease. The present communication deals only with the effect of therapy upon this central nervous system degeneration as observed in 45 patients under treatment in this hospital for 7 years. It was prompted by the recent simultaneous appearance of two papers[1,2] dealing with this problem from different clinics in the United States in which considerable difference of opinion was expressed.

Material for Study. During the 7-year period from 1928 to 1935, 94 cases of pernicious anemia were treated at this hospital. All of these cases were thoroughly investigated clinically and in the laboratory. All showed an initial characteristic response to liver or its equivalent as measured by reticulocyte curves and weekly erythrocyte and hemoglobin estimations. However, of this number, only 45 are available for the purposes of this study because the remainder were observed by us only during what might be termed the hematopoietic recovery period. Following restoration of the blood values they were referred to their family physicians or otherwise disappeared.

The Nature of the Nervous Lesions in Pernicious Anemia. There appears to be as little unanimity of opinion in regard to the nature of the nervous lesions in pernicious anemia as there is of the effect of therapy upon them. It is now generally conceded that practically all cases of the disease show signs of subacute combined degeneration of the cord. If untreated, this degeneration ultimately pro-

gresses to a true sclerosis which from its very nature precludes successful therapy. Hope of success then lies in arresting the process of degeneration before the sclerotic stage is reached. The disease may also cause degeneration in the cerebral cortex, the basal ganglia, or the extradural spinal ganglia. The cause of the degeneration is closely linked up with the cause of pernicious anemia because other anemias, severe in degree, hemolytic in nature, and of long duration, do not develop subacute combined degeneration. The belief recently expressed by a prominent neurologist that some lecithin destroying noxa is responsible for both anemia and nerve degeneration is no longer tenable as pernicious anemia is not now regarded as primarily a hemolytic process. Furthermore, other undoubted hemolytic anemias are exempt from nerve lesions. Histologic studies have revealed perivascular round celled infiltration preceding and accompanying degeneration in affected sensory and lateral tracts, but such a cellular reaction is found in many diseases of the brain and cord and is in no way specific. It is to be hoped that the recent experimental production of a deficiency disease in hogs, which simulates very closely both the blood and nervous system lesions in pernicious anemia, may cast some light upon this fundamental problem.[3] In this series of 95 cases there were 6 deaths but only 2 cases died in the hospital and in only 1 was permission to study the brain and spinal cord granted.

Case Report. CASE 1.—This patient, a male, aged 58, had a paraplegia of at least 3 years' duration with progressive cerebral deterioration. He had received little or no specific therapy during this time and died in a state of grave anemia. At postmortem the organs showed the usual changes found in the disease; anemia of all organs, fatty degeneration of the myocardium and an intensely hyperplastic bone marrow. Sections of the cord and spinal ganglia stained by the Weigert-Pal method showed almost entire demyelinization of the posterior columns in the cervical region, decreasing in degree toward the lumbar segments. The cell bodies in the spinal ganglia and the posterior horn cells were well preserved. The brain showed no lesions. In spite of exaggerated reflexes and spasticity of the extremities suggesting extensive lateral as well as sensory tract involvement little or no evidence of degeneration was present in the motor tracts. The accompanying microphotograph is from a section of the cervical cord stained by the Weigert-Pal method. It shows extensive demyelinization of the columns of Goll and Burdach with other tracts relatively intact.

In this series of cases only one failed to show evidence of subacute combined degeneration of the cord at the time of the first visit, despite the fact that dysesthesia was not accepted as indicative of nerve degeneration. The frequency with which numbness, tingling or pins and needles sensations are met with in severe anemias of whatever etiology or in vascular diseases unassociated with anemia renders these subjective symptoms of little diagnostic value. They were present at some period in practically every case in this series. The following table gives the incidence of certain signs referable to nerve degeneration in the 45 cases.

TABLE 1.—SIGNS INDICATING NERVE DEGENERATION ON ADMISSION.

1. Number of cases		45
2. Diminution in two-point discrimination or vibration sense		44
3. Diminished two-point discrimination		38
4. Diminished vibratory sense alone		42
5. Normal tendon reflexes		28
6. Absent tendon reflexes		9
7. Exaggerated tendon reflexes		8
8. Babinski phenomenon		9
9. Involvement of bladder or rectum		3
10. Cerebral degeneration	Psychosis	3
	Melancholia	1

The evidence of subacute combined spinal degeneration in this series is based mainly upon alterations in two-point discrimination and vibratory sense. Other sensory changes, though sometimes recorded, were too infrequently described and too uncertain to be gauged with any degree of accuracy. It is worth noting that less than half the cases showed alterations in the tendon reflexes or other signs of cord involvement. Only 8 cases had exaggerated reflexes and incoördination, indicating lateral tract involvement. However, it should be recognized that the true incidence of degeneration in the lateral tracts is much higher than these figures indicate for the following reason. The sensory degeneration, present in practically all cases, leads to ultimate loss of tendon jerks if it is not arrested by therapy. Lateral tract degeneration as a rule tends to produce the opposite effect, namely, increased muscle tone with exaggerated reflexes. It seems evident, therefore, that the signs of coëxisting lesions in posterior and lateral spinal tracts would tend to offset each other insofar as the tendon reflexes are concerned. This may account for the high incidence of normal tendon reflexes in cases which obviously show profound functional impairment as indicated by their gait and incoördination of movement. In this series 4 cases who came under observation because of the subacute combined degeneration showed little or no anemia at any time. Blood smears nevertheless showed a definite macrocytosis in all 4. A definite psychosis occurred in 3 cases. In 1 there was definite hypomania with disorientation and bilateral papilledema so marked as to raise the question of an intracranial neoplasm.[4] Another case presented similar findings without papilledema. In both of these cases the cerebral signs and symptoms appeared during the period of anemia and disappeared promptly with restoration of the normal erythrocyte count. In the third case, melancholia appeared during a period when the blood values were well within normal limits.

The Effect of Therapy Upon the Central Nervous System Degeneration. Table 2 gives in abstract the more important changes which occurred in certain signs referable to degeneration in the central nervous system over periods of treatment varying from 1 to 8 years. It also shows the average blood values during the same periods, the

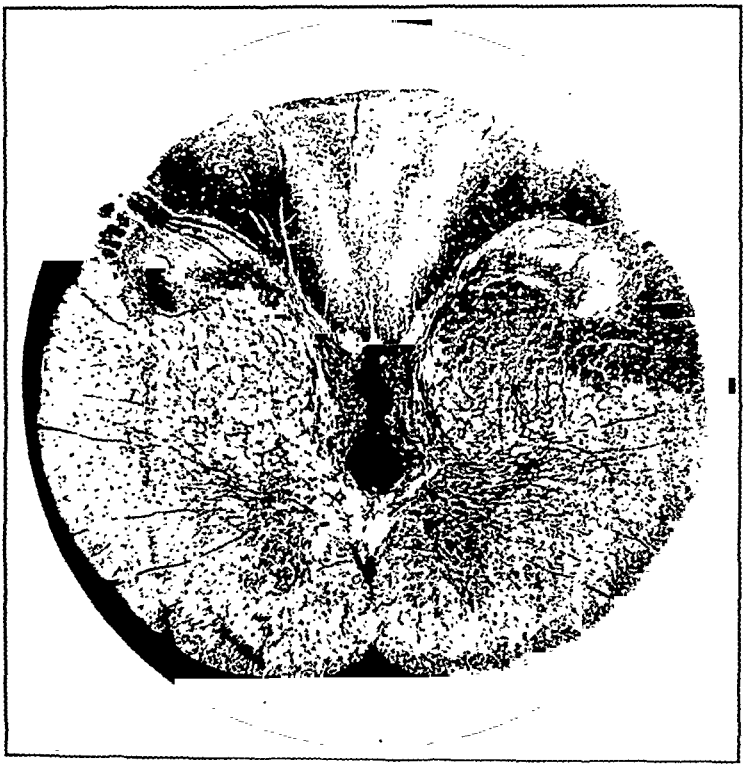


FIG. 1.—Cross section of cervical cord (Weigert-Pal) showing extensive degeneration in posterior columns but none in the lateral tracts.

diameter of the modal erythrocyte, and a rough estimate of the degree of the disability of the patient.

The duration of treatment was as follows:

One year	9	Five years	10
Two years	9	Six years	1
Three years	6	Seven years	3
Four years	4	Over seven years	5

In order to evaluate fairly the remote results of therapy, the initial period of hematopoietic recovery lasting from 6 to 8 weeks was omitted, though subsequent periods of anemia, if any, were included. For comparison the cases were divided into two groups. The cases who received continuous and adequate therapy are compared with the remainder who through apathy, financial or other reasons failed to receive more than sporadic periods of treatment. Before comparing these two groups, however, it is necessary to define the term adequate therapy. It seems generally recognized that no definition should be based upon actual quantities of liver or its equivalent, for cases vary tremendously in the degree of response to a given amount of treatment. Some are relatively resistant and require large doses while others do well on much smaller amounts, just as one case appears to be a relatively mild one with long natural remissions while another is severe with frequent and marked exacerbations. Furthermore, what is considered as adequate therapy in one clinic fails to measure up to the standards set by another. For instance, a recent author[1] expressed the belief that cord degeneration progresses regardless of treatment and that treatment in excess of that amount necessary to maintain an erythrocyte level of 4 millions is "wasted." At another clinic,[2] improvement was noted in the subacute combined degeneration in a modest proportion of cases if the blood count was maintained at or above the 4.5 million level. Such conclusions suggest that better results may be obtained by keeping the blood count as near normal as possible. It has been the custom in our Hematologic Clinic to carry therapy somewhat further. Three fundamental rules for adequate therapy have been followed: 1, The erythrocyte count must be normal at all times; 2, the modal erythrocyte diameter must be at or below the normal value; macrocytosis is considered "ipso facto" an indication of failure of treatment; 3, therapy is at once increased if at any time the patients complain of any deviation in their state of well-being and particularly if there appear any symptoms referable to the nervous system as dysesthesia, etc. This increase is often made in spite of normal blood values. These periods are usually infrequent and may be regarded as an indication of a possible exacerbation of the disease.

Adequate therapy then strives to achieve two results: (*a*) to prevent numerical and particularly morphologic blood changes and (*b*) to

TABLE 2.—BLOOD PICTURE AND NERVOUS SYSTEM CHANGES AFTER TREATMENT.

Name.	Sex.	Age	Blood.			C. N. S. changes.				Year.	C. N. S. changes.				Year.	Remarks.
			R. B. C.	Hb.	C. D.	Ref.	V. S.	T. P. D.	Bab		Ref	V. S.	T. P. D.	Bab.		
1 Alc.	F.	63	4,6	82	7,5	N	75–75	10–19	O	1928	N	0–75	0–11	O	1935	Onset, 1924; no disability.
2 Bar.	M.	58	4,8	89	8,2	E	0–50	0–18	P	1933	E	0–0	0–0	P	1935	Dead.
3 Bar.	F.	65	4,5	90	7,6	N	0–0	Poor	O	1930	N	50–50	5–5	O	1935	No disability.
4 Bas.	M.	53	3,2	91	9,2	A	80–100	16–14	O	1930	A	50–50	15–14	O	1932	Partial disability.
5 Bel.	F.	60	3,9	92	8,4	N		...	..	1934	A		...	..	1935	Helpless.
6 Bat.	F.	40	5,6	82	7,1	E	40–40	9–6	O	1934	N	40–40	9–5	O	1935	No disability.
7 Bla.	M.	56	5,4	86	..	A	0–0	14–14	P	1933	N	25–25	11–13	O	1935	Walked after 1 year's treatment. Slight disability.
8 Bla.	F.	49	4,6	78	7,7	N	0–0	16–20	O	1932	N	80–80	14–11	O	1935	No disability.
9 Bro.	F.	59	4,3	75	8,0	N	0–0	...	O	1932	E	0–0	0–0	O	1935	Little disability.
10 Duf.	F.	42	4,7	85	7,3	N	100–100	15–15	O	1930	N	75–75	5–5	O	1935	No disability.
11 Ell.	M.	39	4,0	72	7,9	E	60–75	14–12	P	1930	E	30–30	9–18	P	1935	Onset 1926; helpless.
12 Esn.	M.	68	4,5	95	7,4	N	0–50	0–11	P	1930	N	60–50	11–15	O	1935	Learned to walk.
13 Fee.	M.	59	4,9	80	7,5	A		...	O	1934	N	50–70	11–10	O	1935	No disability.
14 Fer.	F.	69	4,9	90	7,3	N	100–100	7–7	O	1934	N	40–60	8–8	O	1935	No disability.
15 For.	F.	58	3,5	80	8,1	A	75–75	...	O	1929	N	20–10	9–4	P	1932	Helpless.
16 Fou.	M.	57	4,5	77	7,9	E	100–100	17–12	O	1933	E		...	O	1934	No disability.
17 Gib.	F.	68	4,6	68	7,5	N	9–50	13–13	O	1927	N	50–25	5–8	O	1935	Inadequate to 1933; no disability.
18 Gre.	F.	46	4,6	85	7,7	N	0–0	13–13	O	1925	N	50–65	6–6	O	1935	No disability.
19 Gre.	M.	52	5,3	105	7,8	A	10–10	5–5	O	1934	N	50–64	7–8	O	1935	No disability.
20 Gua.	F.	59	4,8	86	7,6	E	25–25	5–15	O	1932	N	25–35	17–16	O	1935	Onset 1931; no disability.
21 Hal.	M.	56	4,0	80	8,0	N	30–50	15–16	O	1932	E	25–35	6–6	O	1935	No disability.
22 Hoo.	F.	53	4,4	80	7,7	N	50–60	5–5	O	1931	A	75–100	5–5	O	1935	Melancholia.

23 Jon.	F.	57	6,0	105	7,3	N	0–0	20–20	P	1933	N	40–40	5–8	O	1935	No disability; learned to walk.
24 LaM.	M.	50	5,0	100	7,7	A	25–25	12–12	P	1930	N	90–60	6–6	P	1935	No disability.
25 Lev.	M.	42	4,2	80	7,7	N	80–80	9–5	O	1935	N	75–100	5–6	O	1935	No disability.
26 Mat.	M.	56	4,8	85	7,7	N	0–0	10–10	O	1930	N	0–0	6–6	O	1935	No disability.
27 Nib.	M.	59	4,6	85	7,7	N	50–50	5–5	O	1931	N	50–50	5–5	O	1934	No disability.
28 Nel.	M.	66	3,5	65	7,8	E	40–40	14–12	O	1931	E	40–40	18–14	O	1925	Some disability; improving
29 Row.	F.	52	3,9	80	8,3	N	90–90	5–5	O	1930	N	20–10	0–0	O	1935	Helpless.
30 Rus.	M.	51	5,0	80	7,6	A	50–0	8–12	P	1933	A	0–0	6–6	O	1935	No disability.
31 Slo.	F.	60	5,1	95	7,6	N	40–40	9–14	O	1934	..	75–75	5–17	O	1935	Partially disabled; improving.
32 Sul	M.	53	4,5	90	7,7	A	10–20	25–20	O	1934	N	30–30	21–22	O	1935	Cardiac; improving.
33 Swa.	F.	83	3,0	66	..	N		...	O	1914	N	0–0	...	P	1933	Dead.
34 Sta.	M.	65	5,1	83	7,8	N	80–80	5–5	O	1934	E	50–70	11–9	O	1935	Partially disabled.
35 Sta.	M.	44	3,2	84	8,4	N	0–80	7–5	O	1931	A	20–20	14–17	O	1935	Began 1925, no disability.
36 Tay.	F.	57	4,2	80	8,0	N	50–65	5–5	O	1930	N	0–0	9–6	O	1935	Was unable to walk; now no disability.
37 Tha.	F.	56	4,5	90	7,6	N	90–60	7–9	O	1928	N	50–50	14–14	O	1935	No disability.
38 Ste.	F.	72	3,8	75	8,8	N	0–0	15–13	O	1928	..		...	..	1934	Dead.
39 Car.	F.	62	4,2	80	8,2	N	0–0	8–8	O	1930	A	0–0	11–17	P	1935	Partially disabled.
40 McR.	M.	63	5,3	112	7,7	E	0–0	18–8	P	1927	E	25–25	17–12	P	1935	Disabled.
41 Fle.	M.	54	4,5	90	7,9	E	50–25	7–6	O	1930	A		0–0	O	1932	Dead.
42 Foy.	M.	51	4,0	80	8,8	N	70–100	12–12	O	1928	A	0–0	0–0	P	1935	Helpless.
43 McC.	F.	39	4,5	70	7,8	N	100–100	5–5	O	1935	N	100–100	5–5	O	1935	No disability.
44 Fox	F.	45	4,5	90	7,6	N	25–25	9–9	O	1933	N	30–30	9–9	O	1935	No disability.
45 Rob.	M.	67	5,0	95	7,2	N	80–80	11–11	O	1933	N	70–50	11–8	O	1935	No disability.

Key. C. D. = Erythrocyte diameter in micra.
Ref. = Tendon reflexes; N—normal; A—absent; E—exaggerated.
V. S. = Vibration sense expressed in per cent right and left side. Tested middle third tibia.
T. P. D. = Two point discrimination expressed in cm. right and left side. Tested middle third lower limb.
Bab. = Babinski reflex; P = present; O = absent.
R. B. C. and Hb. (millions per c.mm. and %) = average of many counts.

prevent the progress of spinal cord degeneration during those periods of exacerbation in symptoms when sudden and swift disintegration of nerve tissues is likely to take place.

In the first or adequately treated group there are 28 cases and in the second 17 cases. The following table gives a condensed résumé of the results in each group.

TABLE 3.—CORD SIGNS IN ADEQUATELY AND INADEQUATELY TREATED CASES.

	Number.	Percentage.
A. *Adequately treated cases*	28	
Cord signs improved	13	46.4
unaltered	11	39.3
progressed	4	14.3
Cases showing functional disability	3	10.7
B. *Inadequately treated cases*	17	
Cord signs improved	3	17.6
unaltered	0	
progressed	14	82.4
Cases showing functional disability	..	82.4
total	3	
partial	5	
none	3	
Cases dead	6	

It may be argued that such a division of cases would tend to place severe cases or those naturally most resistant to therapy in the second group, favoring the first. Theoretically such an argument is perfectly sound. Practically, however, it has been our experience that no case of uncomplicated pernicious anemia resists adequate therapy insofar as the blood picture is concerned. If such appeared to be the case the diagnosis was invariably found to be incorrect. Furthermore, not one of the inadequately treated cases received regular therapy. Failure to report for treatment usually resulted from apathy or financial embarrassment.

The condensed figures indicate that approximately 47% of the cases in the adequately treated group showed improvement in the subacute combined degeneration and an additional 40% showed no tendency to progress. On the other hand, in the group inadequately treated only 17% showed improvement, while 82% showed progressive degeneration. Perhaps more graphic are the percentages of the disabled. In Group A only 3 of 28 cases showed functional disability judged by their inability to perform their daily work in an efficient manner; while in Group B, 6 are dead, 3 totally disabled, 5 partially disabled and only 3 admit to feeling physically fit. The progress in 1 or 2 individual cases may illustrate the slow but definite improvement which may take place.

CASE 24 (aged 50).—Onset of disease in 1924 with severe anemia and incoördination in leg movements. Treated for tabes in 1930 by general practitioner because of absent tendon reflexes, Babinski phenomena, and Rhombergism. In May, 1930, discharged from hospital by wheel chair on diet of raw liver pulp. In July, 1930, reported on crutches, unable to

walk; blood count almost normal; in October had discarded crutches and was walking with aid of cane and ankle supports; in January, 1931, he discarded cane. By July, 1931, he was able to play a few holes of golf. In September, 1932, walked to and from office daily, could dance and play 18 holes of golf. When seen last in November, 1934, he was able to ski, dance and carry on his business as an engineer. It is of interest that the knee jerks returned though the Babinski phenomenon persisted.

CASE 7 (aged 56).—Onset of disease in 1933 with severe anemia, absent reflexes and bilateral Babinski phenomena. Patient unable to walk. After a year's treatment he began to walk with a cane. Seen in 1935 he walked quite smartly and had normal reflexes. The Babinski had disappeared.

Discussion of Results. A comparison of results in the adequately and inadequately treated groups leaves no doubt as to the efficacy of treatment in controlling subacute combined degeneration if therapy is pushed to the point where the patient is symptomatically well and his blood is morphologically normal. Such an undertaking rarely puts excessive demands upon the patient or the physician. Five cubic centimeters of a potent liver extract per week given intramuscularly will suffice for many cases. This can be obtained in Canada at a cost of 25 cents. The penalty exacted by the disease for carelessness in treatment is severe, and often without retrieve. Of the 17 inadequately treated patients 82% were functionally disabled and one-third of them dead, as compared with no deaths and 10.7% partially disabled in the adequately treated group. The improvement in individual cases is even more striking than the combined results as exemplified by the 2 abstracted cases. Such improvement cannot be hoped for in all cases, particularly if complicating factors, such as cardiovascular disease or senility be present.

The improvement, which may occur in cases of subacute combined degeneration of long duration—after 6 years, as in Case 24—is hard to explain satisfactorily, but the fact remains that it does occur not once or twice but in a considerable proportion of all cases. Not only are the patients subjectively improved and able to perform their daily duties more efficiently, but objectively the concomitant pathologic signs improve or even disappear. Thus in 6 cases the knee kicks returned after having been absent for months or years, and in 4 cases plantar flexion replaced a Babinski elicited on many occasions by different observers. Such improvement is unexpected, and can be explained only on the basis of degeneration of nerve tissue without actual destruction. That such degeneration may persist for long periods and yet eventually respond to therapy is, to say the least, surprising; but the fact remains it does occur. The physician should set no limits to the improvement which may occur in the disease if its victim possesses courage and a determination to get well.

Conclusions. 1. Spinal cord degeneration is present in practically all cases of pernicious anemia.

2. Therapy is adequate only when the blood is restored to normal morphologically as well as numerically. Macrocytosis is an indication of failure of treatment.

3. Spinal cord degeneration rarely tends to progress if treated adequately. Striking clinical improvement may occur.

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THE HEART IN MYXEDEMA: CORRELATION OF PHYSICAL AND POSTMORTEM FINDINGS.

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A review of the literature on the heart in myxedema reveals considerable confusion concerning the true nature of the cardiac lesions. Some feel that they are part of the hypothyroid state, while others believe they are purely incidental. Unfortunately the lack of adequate autopsies has prevented a detailed study of the underlying factors, as practically all of the observations have been based solely on clinical examinations.*

The first and probably the most complete pathologic description of the heart in myxedema appears in a review of 20 cases by the Clinical Society of London[1] (1888). The left ventricle was hypertrophied in one-third and in more than half there was an atheroma of the arteries. A fibrous myocarditis was found in 3 of the 9 cases examined microscopically. Some doubt may be thrown on the proper selection of their material owing to a lack of knowledge of glandular disturbances at that period.

At the Massachusetts General Hospital only 5 autopsy records of the heart in myxedema are available. Four of these showed interstitial edema with more or less fibrosis of the heart muscles,

* Gordon's case recently reported, at the 1935 meeting of the Association of American Physicians, in which the increased cardiac shadows and dullness was found to be due to pericardial effusion, illustrates the need for deciding the question of cardiac hypertrophy in myxedema on the basis of pathologic anatomy.—Editor.

and 1 showed fibrosis only. Ohler and Abramson[14] report that only one partial postmortem examination (unfortunately without microscopic studies) is available at Thyroid Clinic of the Boston City Hospital. The heart weighed 335 gm. and there was edema of the epicardial fat and a translucent light-red heart muscle. The aortic arch showed irregular bands of small yellow projections running longitudinally with a few small gray-white opaque scars. No thyroid therapy had been instituted.

In a case reported by Fishberg[3] the myocardium exhibited small scars and there were atheromatous changes in the large bloodvessels as well as in the coronary arteries. Schultz[4] found marked alternations in the nuclei and a granular degeneration of the heart fibers. He also noted the presence of edema between the fibers.

Scholz,[5] on the other hand, considered the pathologic changes in the heart in myxedema as merely coincidental.

Experimentally, removal of the thyroid gland in animals causes gross alterations in the cardiovascular system. Goldberg[6] showed that sheep and goats made cretinoid by removal of the glands developed cardiac dilatation and a flabby myocardium. In 7 of his 18 sheep excessive pericardial fluid was found. Others working on thyroidectomized animals noted in some instances degeneration of the individual muscle fibers of the myocardium and edema of the interfibrillar tissues, and in others evidence of pathologic changes in the pericardial sac. On the contrary Kiski[15] and Brooks and Larkin[16] concluded from their postmortem studies on animals that the cardiac signs and symptoms produced as a result of hypothyroidism were not due to alterations in the heart muscle.

The first intensive clinical study of the heart in myxedema was made by Zondek[24] in 1918. He found diffuse cardiac enlargement, occasionally limited to the left side and by fluoroscopy he noted sluggish muscular contractions of the enlarged heart which returned to normal after thyroid therapy. Many other authors notably Meissner,[25] Zins and Rösler,[26] Eppinger,[33] Holzman,[27] Ziskin,[28] Ayman,[29] Davis[30] and Fahr[17] have reported cardiac enlargement as a feature in myxedema. In Fahr's publication he cited in detail a case with a shrinkage of 6.3 cm. in the transverse diameter over a period of 7 weeks' treatment with thyroid extract. Previous administration of digitalis was unavailing but under glandular therapy not only was there an actual decrease in the cardiac outline but all signs and symptoms of decompensation disappeared. Lerman, Clark and Means[2] believe that myxedema heart in the sense of cardiac enlargement which undergoes shrinkage on thyroid medication (so-called "accordion heart") is common; in the sense of Zondek and Fahr (*i. e.*, cardiac enlargement in association with congestive failure) it is rare.

In contrast to these views, Willius and Haines[18] believe that gross cardiac enlargement is only an occasional accompaniment and not

a common feature in myxedema. In their study of 162 myxedema patients 91% showed no signs or symptoms of cardiovascular disease. The remaining 9% had cardiac disturbances which could be accounted for in their opinion on grounds other than a low thyroid function. Unfortunately their conclusions are not based on any roentgenologic examinations of the heart.

In addition to the work on the size of the heart numerous observations on the vascular system with special reference to the association of anginal attacks with myxedema have been made. Hertogbe[19] in 1914 suggested that the pain was due to a myxedematous infiltration of the nerve cells of the supporting connective tissue. Sturgis[21] and Whiting and Sturgis[20] thought that arteriosclerosis was a factor in the causation of the anginal syndrome but felt that the associated anemia was of extreme importance because of the resulting added strain on the heart.

Means, White and Krantz,[22] Abrami, Brule and Hietz[23] believed that the attacks of angina may be the result of thyroid therapy, particularly in cases associated with arteriosclerosis. It was the opinion of these observers that the production of pain was due to an increased flow of blood following the use of thyroid where there was an arteriosclerotic narrowing of the coronary vessels.

There is little mention in the literature concerning the relationship between myxedema and hypertension. It apparently may coexist but is not necessarily a part of the clinical picture.

Several writers have limited their reports to electrocardiographic studies. Most of them have corroborated Zondek's original findings in which he emphasized flat *P* waves, flat or inverted *T* waves, and low *R* waves. These changes were interpreted as a result of the diminution in the strength of contractions of the auricle and ventricle inherent in myxedema. In 2 cases Chini[13] found the typical coronary *T* wave described by Pardee. There is a general impression that when these changes occur they will return to a normal graph in the majority of cases following thyroid therapy.

Clinical Observations. In 1925 the writer[32] reported a series of 25 cases of myxedema. Since that time 2 of this group have developed cardiac manifestations which form the basis of this study. A brief résumé of their clinical course and subsequent postmortem findings follows:

Case Reports. CASE 1.—A white female, aged 53, was first seen in 1925 complaining of marked weakness. At that time she had been confined to her bed for several weeks presumably with heart disease. Her mental faculties were dull and she was more or less semicomatose. Her skin was dry but there was no edema. Aside from distant heart sounds nothing of significance was found in her circulatory system. Her blood pressure was 125/80 and her B.M.R. was −28. After thyroid therapy there was a prompt response resulting in a complete remission of symptoms. She found from experience that a discontinuance of the thyroid would cause a return of her discomfort. Her last illness followed a 2 months' interruption

of treatment and on admission to the hospital she was markedly dyspneic, semicomatose and anemic. There was evidence of cardiac enlargement and a small amount of fluid at the right base. Pulse, 80; respirations, 36; blood pressure 110/70. The liver extended to the level of the umbilicus but there was no edema of extremities. Hbg. 55%; red blood cells 2,560,000; white blood cells 7600. Blood urea 80; chlorids 380; serum calcium 7.6; *Wassermann* and urinalysis tests negative; B.M.R. −18 (after 1 week of thyroid treatment). Roentgen ray of chest showed a much enlarged heart. Its greatest transverse diameter was 21 cm. After 2 weeks of thyroid therapy the transverse diameter was 17½ cm., or a shrinkage of 3½ cm. during which time there was a clinical improvement. Fluid was present at the right base. While still in bed precordial pain developed followed later by evidences of coronary occlusion, thrombi in left brachial artery, heart block, cardiac decompensation and death. During her entire illness the respiratory rate continued above 40 per minute. Prior to the last few days, the pulse had a regular rhythm and good volume at 75 to 80 per minute and her blood pressure averaged 110/70. Electrocardiographic tracings on admission showed a normal rhythm, but a negative *T* wave in Lead I. A week later the *T* waves in Lead I continued inverted and there was an increase in rate. At the end of the second week there were further *T* wave and amplitude changes and in addition there was a varying *P–R* conduction time. These abnormalities were followed later by marked changes in the *Q–R–S* and *T* complexes. The final tracings showed a migratory *P* wave with still greater amplitude changes and slurring of the *Q–R–S* complexes. Thyroid therapy was continued during the greater part of her illness and was supplemented by digitalis for a short period following the second tracing.

Autopsy (Dr. J. S. Horsley, within 1 hour after death). About 500 cc. of fluid was found in both pleural cavities but none in the pericardial sac.

Heart somewhat hypertrophied (400 gm. after fixation) and attached over most of its apical half by firm adhesions, with blotchy hemorrhagic patches, to the pericardium. On cutting away the latter the rest of the epicardium was seen to be smooth and shining, except for a large white milk spot over the left auricle. The subepicardial fat was moderate in amount. All coronary arteries were much thickened. On section the left ventricular wall, when traced toward apex, showed a gradual transformation to fibrous tissue, which at the apex was only 3/16 inch thick. Attached to the whole apical half of the cavity was a huge thrombus, almost filling the cavity. Another firm thrombus filled the left auricular appendage. The aortic and mitral valves showed patchy yellow sclerosis of moderate degree (Fig. 1).

Microscopically, at the apex the changes were those commonly found in the fibroid myocardium of coronary arteriosclerosis, but of a most advanced type, *i. e.*, the fibrosis was more marked, and the muscle more atrophied than usual, the latter in fact having almost disappeared. Attached to the inner surface were layers of fibrin almost cell-free (Fig. 2).

Case 2.—A white female, aged 55, was first seen in 1925, complaining of weakness and swelling of extremities. Her physical examination was essentially normal at that time with the exception of a B.M.R. of −33. Her symptoms disappeared under thyroid treatment although a discontinuance of glandular therapy would cause a return of her discomfort. During one of these intermissions 4 months before admission to the hospital she had an episode typical of coronary occlusion, from which she made a slow but satisfactory recovery. No thyroid was given during this period. Her symptoms necessitating hospitalization for her second illness began 2 weeks previously with dyspnea, swelling of the legs and weakness. On examination her heart was enlarged but there was normal rhythm. Pulse 86;

respiration 36; blood pressure 140/90. There were physical signs of fluid at both bases and edema of both legs. Her liver extended a hands' breadth below the costal border. Roentgen ray of the chest showed an enlarged heart having a transverse diameter of 18 cm. Electrocardiogram on admission showed diphasic T waves in Leads I, II, III and IV and isoelectric T in Lead II. One week later T_1 and T_2 were positive, T_3 diphasic and T_4 isoelectric. Hgb. 60%; red blood cells 3,342,000; white blood cells 12,400; chlorids 840; globulin 2.2; albumin 3.6; creatinin 5.1, mg. per 100 cc. blood.

There was only a slight decrease in the size of the heart shadow during her illness and very little response to thyroid therapy. Dyspnea was the outstanding symptom which seemed to be out of proportion to the amount of circulatory disturbance. Evidence of further coronary involvement developed which apparently caused her death.

Autopsy (Dr. J. P. Baker, Jr., within 1 hour after death). Several hundred cc. of fluid was found in the right pleural cavity, but none in the pericardial sac.

A moderately hypertrophied heart (450 gm. after fixation), with smooth glistening pericardium, increased subepicardial fat, and extremely sclerosed coronary arteries, the lumina of which are reduced to pin-point size. On section, the entire apical half of the left ventricular myocardium shows nearly complete replacement of fibrous tissue, the thickness of this at the apex being about $\frac{1}{8}$ inch. Firmly attached to the apical third of the endocardium is a hard white thrombus. The mitral and aortic valves are unaffected. The right cavities and left auricle appear normal (Fig. 3).

Microscopically, at the apex the changes found were those typical of fibroid myocardium in coronary arteriosclerosis, but were of a most advanced kind. Epicardium and fat were normal. The myocardium was reduced to one place to about $\frac{1}{10}$ inch thickness, and everywhere about the apex was largely replaced by fibrous tissue with small islands of isolated muscle fibers in various stages of atrophy and degeneration. The small vessels, branches of the anterior descending coronary, were thickened to a marked degree. Attached to the endocardium were layers of fibrin containing little or no red cells, for a considerable thickness. The left coronary artery, about an inch distal to its origin was reduced in diameter to less than one-third, the walls being enormously thickened by crystallin material (Fig. 4).

Discussion. Although the term myxedema heart is accepted by most observers there is a wide difference of opinion as to whether the apparent increase in size of the cardiac shadow is due to pericardial effusion, dilatation, actual hypertrophy or a type of myocardial flabbiness resulting from a low metabolic rate. Lerman, Clark and Means[2] found fluid in the pericardium in their 2 autopsied patients who had not received thyroid before death, but aside from its occurrence in part of Goldberg's experimentally produced myxedemas in sheep, it has not been a prominent feature. Actual hypertrophy with or without dilatation was present in the majority of the other authentic postmortem records and has been a frequent finding by Roentgen ray in the clinical records.

It is reasonable to presume that the microscopic findings in these cases would vary according to the stage of the myxedema as well as to whether thyroid therapy had been in progress prior to the death of the individual. The presence of a mucin-like infiltration



FIG. 1.—Myxedema heart (400 gm. after fixation), showing almost complete fibrosis toward apical region. Black line indicates the cut edge of the endocardium. A fresh thrombus is seen *in situ*.

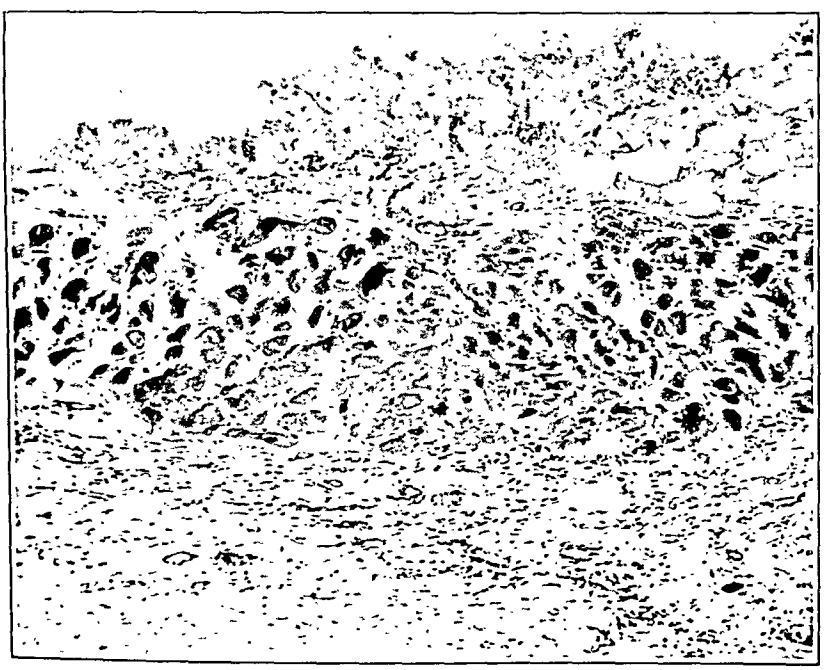


FIG. 2.—Microscopic section of myxedema heart showing muscle degeneration and fibrosis near apex. (× 100.)



FIG. 3.—Myxedema heart (450 gm. after fixation), showing replacement of muscle with fibrous tissue and a fresh apical thrombus. Black line indicates the cut edge of the endocardium.

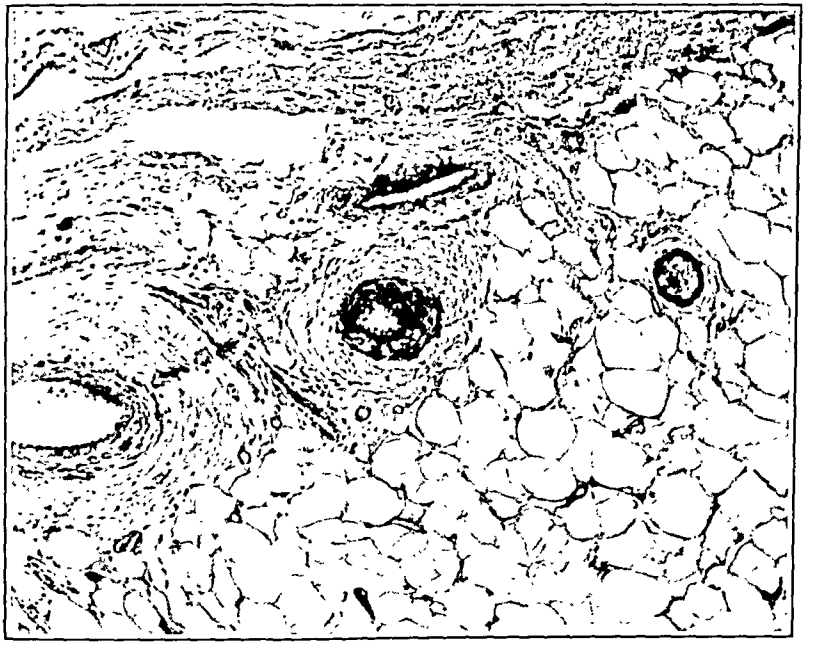


FIG. 4.—Microscopic section of the heart taken near the apex showing fibrosis, and extreme coronary occlusions. (× 100.)

in the myocardium in the untreated individuals is not incompatible with the finding of granular degeneration and fibrosis in one where thyroid had been administered. The frequent reference to arterial changes in these studies and the well-known presence of arteriosclerosis in the clinical records of myxedema are worthy of a more detailed discussion.

There appears to be a striking analogy between the occurrence of arteriosclerosis in diabetes and spontaneous myxedema. In both instances the sclerotic process often begins early in the disease regardless of the age of the patient, and is one of the most constant findings in both maladies in their terminal stages. In a recent survey of vascular complications in diabetic individuals dying in New York City during 1930, more than half of the deaths were attributable to cardiovascular diseases. Of 100 diabetic patients past the age of 40 Enklewitz[11] found that 79 had arteriosclerosis of the aorta and 70 showed the same process in the kidneys. Coronary thrombosis occurred twice as frequently in diabetic as in non-diabetic patients. Joslin[12] states that the evidence implies that the increasing incidence of arteriosclerosis in the diabetic individual can be checked and the earlier types of arteriosclerosis overcome by a diet which provides for a complete oxidation of fat.

The analogy between these two diseases is further borne out by the constant finding of a high cholesterol in both conditions. The presence of hypercholesteremia in myxedema is so invariable that it is now regarded as a more reliable index of thyroid underactivity than even the basal metabolic rate. Although the etiologic factors entering into the development of arteriosclerosis are not definitely established, none has a more convincing experimental basis than the rôle of the cholesterol esters. Many years ago Virchow suggested the relationship of abnormal fatty metabolism to these vascular changes and more recently Aschoff[8] has modified it. According to his conception, there is a fatty deposition in the walls at the site where vessels are under physiologic strain. These lipoid substances apparently are derived from the blood and reach the intima by way of the lymph to be precipitated in the fine meshwork of the intermediate elastic layer. As the cholesterol esters becomes more concentrated in the blood stream there is an increasing imbibition of these lipoids into the vessel walls. The greater the accumulation of lipoids in the interstitial tissue the more obvious does the presence of droplike deposits in the cells of the intima become. There is experimental evidence to show that every lipoid infiltration of the intima when it has been present a sufficient time causes a reactive hypertrophy of the adjacent intimal tissues. As a result of this superconcentration of lipoids areas of necrosis develop which in turn are followed by a deposition of calcium salts.

Anitschkow[10] has described lesions of the vessels which he believed to be true arteriosclerosis in certain animals obtained with a diet rich

in cholesterol. These findings have also been confirmed by Newburgh and Clarkson.[9] Shapiro[31] was able to produce arteriosclerotic changes and a hypercholesterolemia in rabbits by thyroidectomy and a high cholesterol diet. Although this experimental arteriosclerosis shows certain definite variations from the human type, it is sufficiently close to be of clinical significance particularly in those diseases associated with a high cholesterol in the blood.

Another factor to be considered in the production of the terminal changes in the myxedema heart is the strikingly slow velocity of blood flow in these cases. Blumgart, Gargill and Gilligan[7] have shown that the slowing of the blood flow in myxedema was almost as great as that observed in patients with rheumatic valvular heart disease with auricular fibrillation and congestive failure. The great increase in velocity of the blood that occurs when the basal metabolism rate is raised to normal affords a rational explanation of the clinical manifestations of cardiac insufficiency which not infrequently follow too active glandular therapy in myxedema.

This physiologic breakdown coupled with the tendency to arteriosclerotic narrowing of the vessels justifies the assumption that the coronary system eventually fails to supply the needs of the heart and myocardial incompetence results. The autopsy records of the 2 cases reported bear out this conclusion and offer a reasonable cause for the clinical course in each instance. Other available pathologic studies tend to substantiate this impression. There is, however, a general feeling based largely on cardiac findings following total ablation of the thyroid gland that myxedema heart in the sense of a condition precipitating attacks of congestive heart failure does not exist. In the clinical records of the first patient there is ample evidence of decompensation prior to the development of coronary occlusion. In the second case similar findings were present but they may have been the result of a failing myocardium following a coronary episode 4 months previously. It must be remembered in this connection that whereas spontaneous myxedema is a gradually developing disease over a period of many years the artificial type is of much shorter duration. If abnormal cholesterol metabolism is the chief etiologic factor in the production of the vascular changes found in spontaneous myxedema it is obvious that not sufficient time has elapsed to evaluate its effect on the heart in artificial myxedema.

It may be concluded from the experimental evidence and the available postmortem findings that changes in the cardiovascular system in myxedema are of frequent occurrence. Sufficient evidence has accumulated to make it apparent that the term myxedema includes varying groups of thyroid underactivity. We no longer restrict the diagnosis to the clinical picture originally described by Gull and it is, therefore, not reasonable to assume that similar circulatory findings would be present to the same extent in the incip-

ient as in the advanced types. In the early stages of thyroid deficiency it is probable that there is a mucin-like infiltration of the muscle fibers which can be overcome by the judicious use of thyroid extract. The postmortem findings from the Massachusetts General Hospital and also the one reported by Schultz[4] would seem to indicate that their cases fell in this group.

As the disease progresses further degenerative changes occur and a more advanced pathology is found. This is characterized by a definite enlargement of the heart and the development of sclerotic areas in the arterial vessels. Because of these early and late changes degeneration of the muscle fibers take place to be followed by an extensive fibrosis of the myocardium. The most logical explanation for the resulting arteriosclerosis is the presence of high percentage of cholesterol in the blood. If proper doses of thyroid are selected it is reasonable to believe that further damage to the heart and circulatory system can be avoided. The excessive use, however, of glandular therapy would tend to increase the velocity of the blood through the heart and coronary failure would probably follow.

The heart in myxedema is a distinct clinical and pathologic entity and should be considered in the differential diagnosis of every obscure cardiac disease. It seemingly bears a direct relationship to abnormal cholesterol metabolism and its prevention depends largely on its early recognition.

The pathologic studies on the cases reported in this paper were made by Dr. Frank Apperly, Head of the Department of Pathology, Medical College of Virginia, to whom I am deeply indebted.

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THE PROGNOSIS OF BUNDLE BRANCH BLOCK AND OTHER INTRAVENTRICULAR CONDUCTION SYSTEM LESIONS.

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The purpose of the research reported here is to ascertain life-expectancy in patients who have electrocardiographic evidence of damage to the intraventricular conduction system of the heart. It has been customary to consider these lesions under two categories, bundle branch block and arborization block, but we treat both here under the head of intraventricular block in the broad sense of the term.

Electrocardiograms have been classified as examples of bundle branch block only when they present (1) definite left or right axis deviation, (2) appreciable slurring of the Q–R–S deflections or measurable delay in conduction time of this total complex group over 0.1 second, and (3) T waves pursuing a direction reversed from the major Q–R–S deflection in Leads I and III. Curves demonstrating marked delay in the tracing of the Q–R–S complex group, but failing to fulfill the other criteria mentioned above, have been assembled in a heterogeneous group and designated as examples of intraventricular block.

In a recent report which includes few data on prognosis, Bayley[1] identifies, in addition to the classical "levogram" and "dextrogram" forms, three groups which he believes represent additional examples of "dextrogram" bundle branch block. All of these three sub-groups

present definite slurring of S_1, and prolonged Q–R–S excursion time. Comment will be made later on the statistical justification of this classification.

Electrocardiographic identification of the site of lesion in bundle branch block has been a matter of controversy and the subject of several recent reports. We have termed the commonly occurring type of "levogram form," the left bundle branch block, and the infrequently occurring type of "dextrogram form," the right bundle branch block, according to the scheme of Wilson *et al.*[2]

Graybiel and Sprague[3] have divided the group of intraventricular blocks into three classes: (*a*) the homophasic form, in which the T waves occur in the same direction as the major Q–R–S deflections; (*b*) the indeterminate type, in which the major deflection of the Q–R–S group is in the same direction in all three leads; and (*c*) a group with Q–R–S delay, but not falling into any of the above classifications. According to their data, none of these types was found to differ appreciably in prognosis from the two "classical" bundle branch block groups.

Discussion of Data. The case records analyzed covered the 20-year period from 1913 to 1933, during which time one or more

TABLE 1.—CASES OF BUNDLE BRANCH BLOCK.

Distribution by:	No. of patients.	% of total.	Dead. No. of patients.	Dead. %
Type:				
Left bundle branch block (levogram form)	146	93	109	75 —
Right bundle branch block (dextrogram form)	11	7	10	91 —
Sex:				
Males	96	61 —	76	81
Females	61	40 —	43	71 —
Age groups (at time of discovery of lesion):				
To age 40	14	9	12	85
40 to 49	24	15	19	79 —
50 to 59	49	31	34	69 —
60 to 69	47	30 —	37	80
70 to 79	19	12	15	79 —
80 or over	4	3 —	3	75
Etiology:				
Arteriosclerotic	56	36	43	80 —
Hypertensive and arteriosclerotic	52	34 —	40	77
Syphilitic	14	9	13	93 —
Rheumatic	10	6	8	80
Thyrotoxic	7	5 —	2	29 —
Miscellaneous and doubtful etiology	18	11	10	55
Total	157		121	77

Fatality of 50 patients of whom successive electrocardiographic records were made:

	Electrocardiogram. Unchanged (%).	Showed advancing form (%).	Showed receding form (%).
Case fatality	64 —	80 +	80 —

electrocardiographic records of each of approximately 8000 patients were secured in the laboratory of the University of California Hospital. The data assembled in the accompanying tables and figures include the duration of life in years and in percentages of estimated life expectancy lived as derived from the medico-actuarial estimates in the year 1924, as well as the case fatality rates of patients presenting the lesions under discussion.

Table 1 represents the case fatality rates of the group of 157 patients whose tracings presented examples of classical bundle branch block; and Table 2 those of the heterogeneous group of 112

TABLE 2.—CASES OF INTRAVENTRICULAR BLOCK.

Distribution by:	No. of patients.	% of total.	Dead. No. of patients.	Dead. %
Sex:				
Males	75	67	38	51
Females	37	33	14	38
Age groups (at time of discovery of lesion:				
To age 40	28	25	8	29
40 to 49	24	21	6	25
50 to 59	26	23	14	54
60 to 69	27	24	19	70
70 to 79	5	4	4	80
80 or over	2	2	1	50
Etiology:				
Arteriosclerotic	39	35	25	64
Hypertensive and arteriosclerotic	19	17	10	53
Syphilitic	9	8	5	55
Rheumatic	12	11	8	66
Thyrotoxic	4	4	2	50
Congenital	7	6	1	14
Miscellaneous and doubtful etiology	22	19	3	14
Total	112		52	46

Fatality of 42 patients of whom successive electrocardiographic records were made:

	Electrocardiogram. Unchanged (%).	Showed advancing form (%).	Showed receding form (%).
Case fatality	32−	74+	10−

examples of atypical intraventricular conduction system block. Because no cognizance is taken of the length of time the living patients were followed, these case fatality rates cannot be accepted as an accurate estimate of prognosis. Actually, however, these case fatality rates are close approximations since a great number of patients recorded as dead passed into that classification relatively shortly after discovery of the lesion, at which time most of the living patients were still being followed. Thus, the known fatality was never more than 10% lower than the hypothetical case fatality rate based on the supposition that all the "living" patients had been followed as long as the longest period in each group; namely, 17 years for the intraventricular blocks and 11 years for the bundle

branch blocks. It is likewise recognized that some of the patients who died did not die of cardiovascular disease. The number which fall into this group is known to be too small to affect the case fatality figures.

TABLE 2A.—SUBCLASSIFICATIONS OF INTRAVENTRICULAR BLOCKS.

	Living.	Dead.	Total.	Fatality (%).
I. Left (Graybiel and Sprague's classification)				
A. Homodirectional, left (*T* upright in Lead I)	43	15	58	28
B. Classical form, left bundle branch block (criteria doubtful)	17	10	27	37
C. Mixed type (all *R*'s upright)	13	5	18	28
D. Miscellaneous	8	4	12	33
Total	81	34	115	29

	Living.	Dead.	Total.	Fatality (%).
II. Right (Bayley's classification—all have slurred S_1)				
A. Classical form, right bundle branch block (criteria doubtful)	10	3	13	23
B. R_1 greater than S_1, otherwise the same	8	1	9	11
C. Prominent S_3, with slurred upright wave following it	2	2	4	50
D. Deep S_3, without slurred upright wave following it	7	3	10	30
Total	27	9	36	25

There are added to this group of intraventricular block, 39 cases of "classical" form of bundle branch block and 1 case of intraventricular block that were not entered in either Tables 1 or 2 because the criteria were doubtful. This accounts for the discrepancy in total number of cases in this table (151) as compared with Table 2 (112).

TABLE 3.—BUNDLE BRANCH BLOCK. CHANCE OF SURVIVAL, IN PER CENT, FOR EACH YEAR OF LIFE ATTAINED FOLLOWING DISCOVERY OF LESION.

No. of years patient has survived following discovery of lesion.	Chances patient may survive to end of:										
	1st yr.	2d yr.	3d yr.	4th yr.	5th yr.	6th yr.	7th yr.	8th yr.	9th yr.	10th yr.	11th yr.
Onset	72	66	42	36	30	27	22	21	21	21	20
1	..	73	60	51	40	36	30	28	28	28	27
2	..	..	71	65	52	47	40	35	35	35	34
3	..	..	..	85	78	72	30	46	46	46	44
4	..	..	..	..	80	72	59	54	54	54	51
5	..	..	..	..	..	91	74	68	68	68	64
6	..	..	..	..	..	..	82	74	74	74	71
7	..	..	..	..	..	..	..	93	93	93	89
8	..	..	..	..	..	..	..	..	93	93	93
9	..	..	..	..	..	..	..	..	..	93	93
10	..	..	..	..	..	..	..	..	..	..	98

From the hypothetical case fatality graphs connecting the middle coördinates in Figures 1, 2, 3 and 4, Tables 3, 4, 5 and 6 have been constructed. Tables 3 and 5 give, for each of the groups, the estimated chance of survival, in percentage, for each year of life follow-

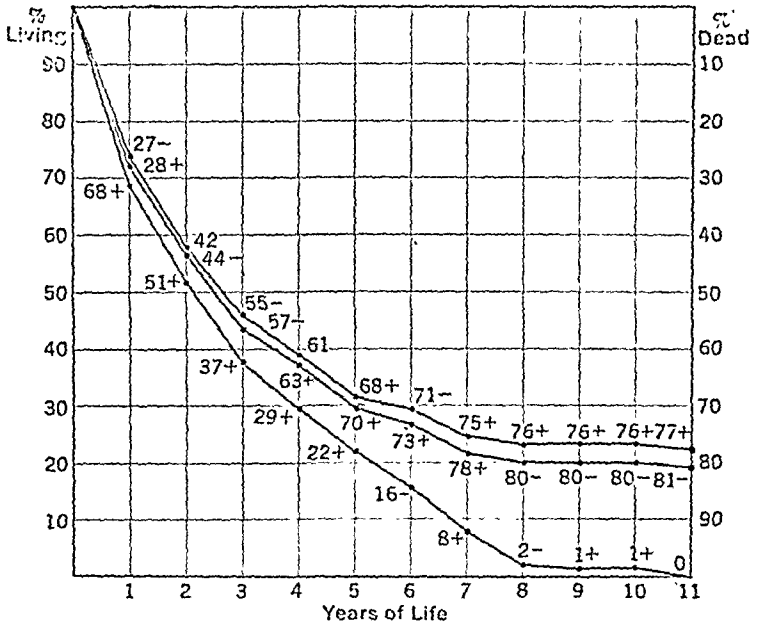


FIG. 1.—Distribution of 157 cases of bundle branch block according to years of life to which they were followed after discovery of the lesion. See descriptive footnote.

LEGEND FOOTNOTE TO FIGS. 1, 2, 3 AND 4.

Figs. 1, 2, 3 and 4 represent the integral curves of the estimated disposition of 100% of the cases in each group, Figs. 1 and 2 of the cases of bundle branch block, and Figs. 3 and 4 of the heterogeneous cases of intraventricular block. The ordinates represent the percentages. The abscissæ of Figs. 1 and 3 indicate the changes that have taken place after each year of life since the discovery of the lesion; while the abscissæ of Figs. 2 and 4 represent the changes that have occurred after each 10% of the theoretical 100% of life expectancy.

The upper curve in each figure connects the points representing the actual percentages of patients known to have died during each successive period. The lower curve connects the points representing the percentage of patients known to be living at the end of each successive period. These percentages drop rapidly, of course, after 5 years' time, reaching 0 at the end of 11 years in the bundle branch block chart, and 17 years in the intraventricular chart, as these were, respectively, the longest numbers of years that any patients in the groups were followed. (Note the intraventricular block chart is carried only to 16 years.)

The middle curve represents estimates of the percentage of fatality in successive periods, including a final estimate for the complete group. The points in the curve have been obtained by applying the known fatality rate of each period to the number of living patients that have dropped from observation during the preceding period. The estimated percentage of fatality of the unobserved patients is added to the fatality rate of observed patients; and a hypothetical percentage of fatality for the entire group is thus obtained.

If a curve-smoothing device had been applied to these graphs, the unusual deviation noted in Tables 3, 4, 5 and 6 based on actual case number calculations would not have occurred. For example, in Table 3 a patient has a 73% chance of surviving to the end of the second year if he survives 1 year after the discovery of the bundle branch block, but only a 71% chance of survival to the end of the third year if he survives 2 years after the discovery of the lesion.

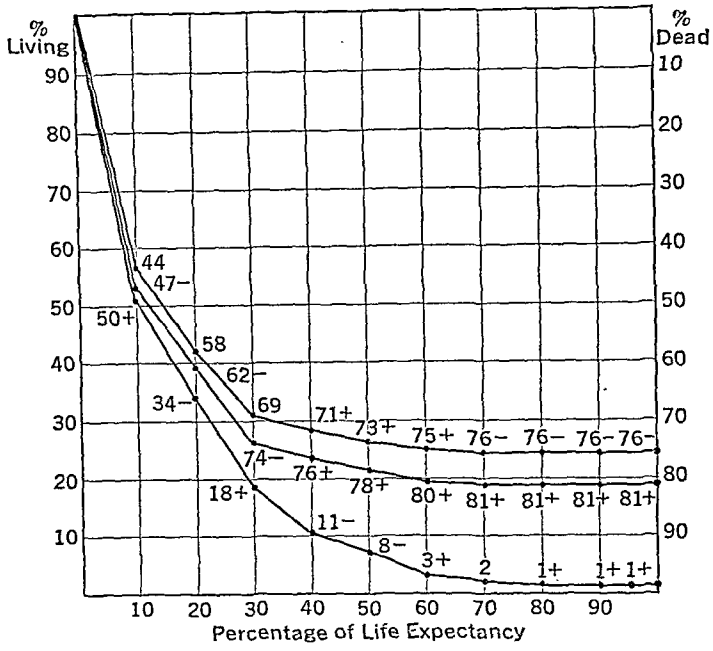


FIG. 2.—Distribution of 157 cases of bundle branch block according to percentage of total life expectancy to which they were followed after discovery of the lesion. See descriptive footnote.

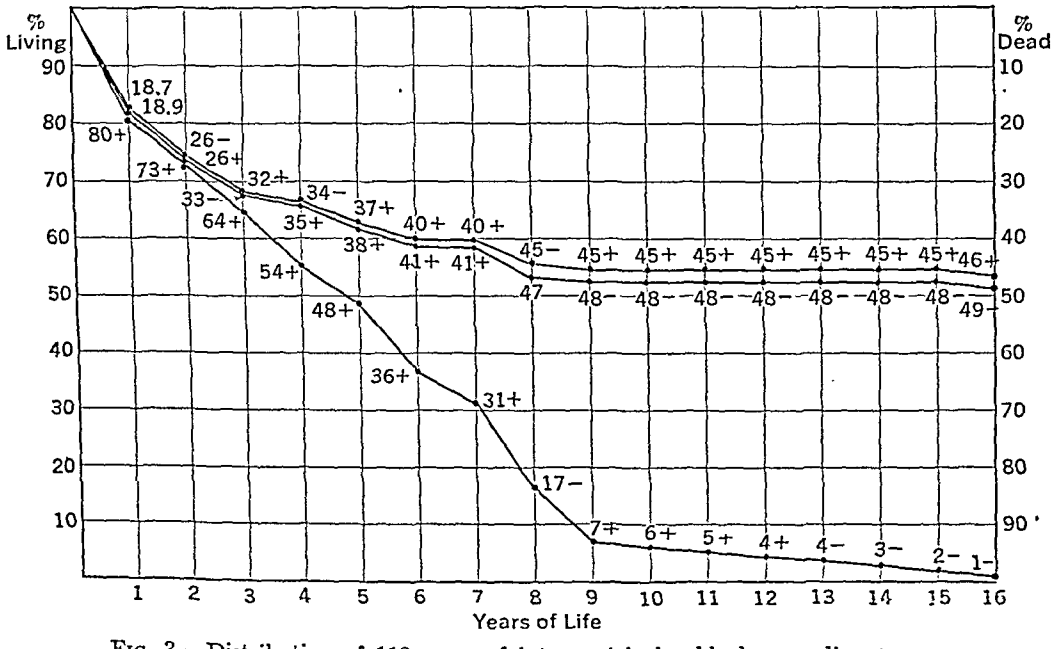


FIG. 3.—Distribution of 112 cases of intraventricular block according to years of life to which they were followed after discovery of the lesion. See descriptive footnote.

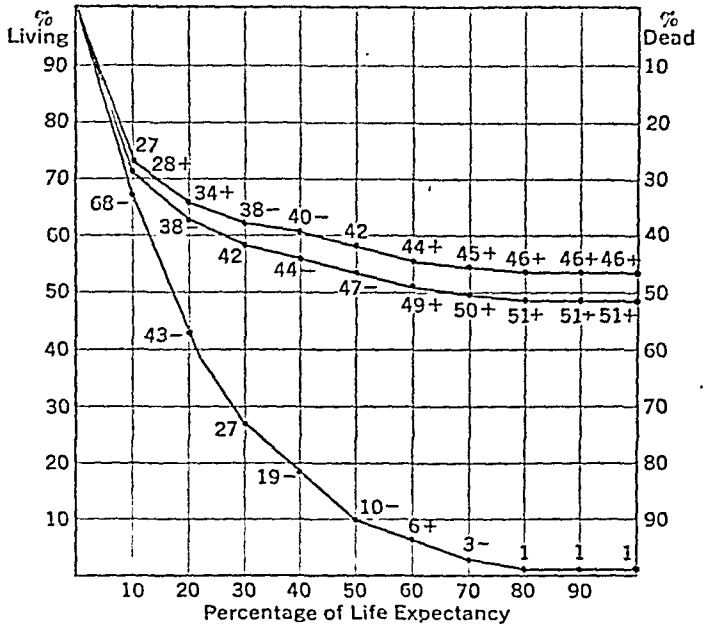


FIG. 4.—Distribution of 112 cases of intraventricular block according to percentage of total life expectancy to which they were followed after discovery of the lesion. See descriptive footnote.

TABLE 4.—BUNDLE BRANCH BLOCK. CHANCE OF SURVIVAL, IN PER CENT, FOR EACH 10% OF LIFE EXPECTANCY ATTAINED FOLLOWING DISCOVERY OF LESION.

Per cent of life expectancy attained following discovery of lesion.	Chances patient may survive to life expectancy of:									
	10%.	20%.	30%.	40%.	50%.	60%.	70%.	80%.	90%.	100%.
0	54	39	27	24	22	20	19	19	19	19
10	..	72	49	43	41	36	35	35	35	35
20	..	..	69	61	56	50	49	49	49	49
30	..	..	..	88	82	73	71	71	71	71
40	..	..	..	..	92	83	81	81	81	81
50	..	..	..	..	..	90	88	88	88	88
60	..	..	..	..	..	..	97	97	97	97
70	..	..	..	..	..	..	..	97	97	97
80	..	..	..	..	..	..	..	..	97	97
90	..	..	..	..	..	..	..	..	..	97

ing the discovery of the lesion. Tables 4 and 6 give the chance of survival, in percentage, for each 10% of total life-expectancy attained following the discovery of the lesion. Thus, in Table 3 it is seen that an individual has, at the time of the discovery of his lesion, a 20% chance of surviving 11 years longer; whereas, if he survives for 3 years, his chance becomes 44% of surviving the remaining 8 years. This remarkable improvement in statistical prognosis, which takes place as time elapses following the discovery of the lesion, is most effectively demonstrated in the tables calculated on the percentages of life-expectancy, since this method of

TABLE 5.—INTRAVENTRICULAR BLOCKS. CHANCE OF SURVIVAL, IN PER CENT, FOR EACH YEAR OF LIFE ATTAINED FOLLOWING DISCOVERY OF LESION.

No. yrs. patient has survived following discovery of lesion.	Chances patient may survive to end of:															
	1st yr.	2d yr	3d yr.	4th yr.	5th yr.	6th yr.	7th yr.	8th yr.	9th yr.	10th yr.	11th yr.	12th yr.	13th yr.	14th yr.	15th yr.	16th yr.
Onset	81	74	67	65	62	58	58	53	52	52	52	52	52	51	51	51
1	..	91	83	81	76	72	72	65	64	64	64	64	64	63	63	63
2	..	..	91	89	83	79	79	72	70	70	70	70	70	69	69	69
3	..	..	..	97	91	87	87	78	77	77	77	77	77	76	76	76
4	..	..	..	..	94	90	90	81	79	79	79	79	79	78	78	78
5	..	..	..	..	..	95	95	86	84	84	84	84	84	83	83	83
6	..	..	..	..	..	..	95	86	84	84	84	84	84	83	83	83
7	..	..	..	..	..	..	..	91	89	89	89	89	89	87	87	87
8	..	..	..	..	.	..	..	..	98	98	98	98	98	96	96	96
9	..	..	..	..	..	..	..	.	..	98	98	98	98	96	96	96
10	..	..	..	..	..	..	..	..	..	..	98	98	98	96	96	96
11	..	..	..	..	..	..	..	..	..	..	..	98	98	96	96	96
12	..	..	..	..	..	..	..	..	..	..	..	..	98	96	96	96
13	..	..	..	..	..	..	..	..	..	..	..	..	..	98	98	98
14	..	..	..	..	..	..	..	..	..	..	..	..	..	..	98	98
15	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	98

TABLE 6.—INTRAVENTRICULAR BLOCKS. CHANCE OF SURVIVAL, IN PER CENT, FOR EACH 10% OF LIFE EXPECTANCY ATTAINED FOLLOWING DISCOVERY OF LESION.

Per cent of life expectancy attained following discovery of lesion.	Chances patient may survive to life expectancy of:									
	10%.	20%.	30%.	40%.	50%.	60%.	70%.	80%.	90%.	100%.
0	72	63	58	56	53	51	50	49	49	49
10	..	87	81	78	75	71	69	68	68	68
20	..	..	93	90	85	81	80	78	78	78
30	.	..	..	92	91	87	86	84	84	84
40	..	..	..	..	94	90	89	87	87	87
50	..	..	..	..	..	96	94	92	92	92
60	..	..	..	..	..	..	98	96	96	96
70	..	..	..	..	..	..	..	98	98	98
80	..	..	..	..	..	..	.	..	98	98
90	..	..	..	..	..	..	..	..	..	98

tabulation discounts the natural fatality chances of the elderly individual. The high case fatality rate for the first year of life after the discovery is thus made obvious. Such fatal cases may represent rapidly developing but not instantaneous occlusion of coronary arteries which in our experience do not often present the picture of classical bundle branch block.

The chance of an individual in the bundle branch block group to survive to 100% of his life-expectancy, rises from 10% to 49% if he survives 20% of the total expectancy after the discovery of the lesion. It is acknowledged that the time of discovery of the lesion is later than the actual onset, but we believe from the shape of the curves in Figures 1, 2, 3 and 4 that the majority of the onsets is close to the times of discovery.

Several interesting observations may be made from the data recorded in Tables 1 and 2, as follows:

1. In comparing these data with those recently published by Graybiel and Sprague[3] who had 308 patients followed for an unknown period (from 16,000 records of the Massachusetts General Hospital), the following is noted: They obtained 75 examples of classical left bundle branch block and 19 of right bundle branch block (total 94), and 214 examples of the three atypical intraventricular block groups; whereas, among our cases there were 146 left bundle branch blocks and 11 right bundle branch blocks (total 157), and only 112 cases of atypical intraventricular defects. Their case fatality rate was approximately constant, numerically:

	% Dead.
Right bundle branch block	67
Left bundle branch block	77
Atypical group	74

as compared with our cases:

	% Dead.
Right bundle branch block	91
Left bundle branch block	75
Atypical group	46

2. The case fatality rate of the females was definitely lower than that of the males, in both of our groups.

3. In the cases of bundle branch block which were reviewed, a large number occurred in the involutionary decades of 50 to 60, and 60 to 70 years of age; whereas the cases of intraventricular block were fairly uniformly distributed to the age of 40, and materially diminished in number during the decades following.

4. The case fatality rate was found to be nearly uniform in both groups. That of the bundle branch block group was slightly higher in the early years. In the group of intraventricular blocks, the fatality was quite low in the early decades, but approximated the fatality of the group of bundle branch blocks in the later decades, indicating that when the etiology is arteriosclerosis, the significance of both lesions was the same.

5. Congenital heart disease produced no typical bundle branch blocks, only atypical forms; and these attendant electrocardiographic changes held no prognostic significance.*

6. The group of doubtful etiology had a relatively low fatality rate and probably represented cases of small focal lesions in the heart without general damage, and, therefore, insufficient symptoms or signs to point toward a definite etiology.

7. Among the luetic cases there was a much higher case fatality rate in patients presenting bundle branch block than in those with intraventricular block, the former being the highest fatality of any group assembled (93%).

* One instance of typical right bundle branch block was observed in a patient with congenital heart disease who died by suicide. This is not included in our series of 157 cases.

8. Owing to the controversy as to whether or not thyrotoxicosis can cause organic cardiac disease, it is of interest that several of the patients in both groups reported under thyroid heart disease were under the age of 45 and had no proven evidence of any other etiologic agent. Those patients over the age of 45 may have had coronary arteriosclerosis contributing toward the cause of intraventricular or bundle branch block defects. There was one patient in whom definite myxedema was present. Approximately the same case fatality rate existed in this as in other etiologic groups.

9. In the group of bundle branch blocks, patients with successive records showing no change had a lower fatality than patients whose electrocardiograms showed either advances or recessions from the extreme typical form of bundle branch block; but in the intraventricular block group the lowest fatality was found among patients whose electrocardiograms had indicated recession from the form of a bundle branch block. There was no constant interval between successive records in the same or different patients and the changes were estimated on arbitrary criteria. Such data probably have little significance.

10. In the subclassification of intraventricular blocks according to Bayley's[1] scheme, we find the case fatality rates uniformly lower than in the classical bundle branch block forms. From this evidence it would seem more reasonable to continue classifying these forms with the less serious heterogeneous group of intraventricular blocks.

Conclusions. One hundred and fifty-seven cases of classical bundle branch block and 112 cases of heterogeneous atypical intraventricular conduction-defect (as demonstrated by electrocardiograms), have been reviewed in an effort to estimate the prognosis of these groups.

Certain prognostic findings seem to characterize these groups and their elements. Especially to be noted is the high fatality occurring in cases of bundle branch block during the first year after the discovery of the lesion or in the first 20% of the life-expectancy and the remarkable diminution of the case fatality rate in the groups which survive these periods.*

* At time of publication 1 case of left bundle branch block was still in reasonably good physical health 12 years after the discovery of the lesion.

We wish to thank Dr. William J. Kerr for the use of material and C. M. Rose and R. E. Sampson for assistance in case follow-up.

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AN ELECTROCARDIOGRAPHIC STUDY OF LEAD IV WITH SPECIAL REFERENCE TO THE FINDINGS IN ANGINA PECTORIS.*

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As a result of very elaborate theoretical work by Wilson and his collaborators[1] culminating in some clinical observations[2,3] and amplified by the studies of Wolferth and Wood[4,5,6] precordial leads have been introduced into the electrocardiographic study of heart disease. The main emphasis has been on the detection of changes indicating myocardial infarction. Although this procedure has been in use only for a few years, alterations in the electrocardiogram have been observed by this method that have confirmed the diagnosis of coronary thrombosis made by the more usual means and at times has constituted the only reliable evidence of such diagnoses.[2–11] In general it has been found that when one electrode is placed over the precordium and the other or indifferent electrode is placed on the back or left leg, the ventricular complex of a normal heart will show a sharp initial downward deflection ($Q4$) and an inverted T-wave.[12,13] It has been emphasized that during the acute stages of myocardial infarction the Q–T interval may be significantly depressed below or elevated above the isoelectric line depending upon whether the lesion is in the anterior or posterior portion of the ventricle respectively. With anterior lesions it has also been noted that the Q-wave generally disappears entirely so that the initial ventricular deflection is directed upward. In posterior lesions the Q-wave is expected to persist. Simultaneous the T-wave of Lead IV which normally is inverted may become upright in anterior lesions and the inversion may be exaggerated with posterior involvement. The alterations of the T-wave when they do occur can be temporary so that an essentially normal form may be eventually resumed. Wilson particularly has emphasized the more permanent changes in the Q–R–S complex in contrast to the transient alterations in the T-wave. Although this has been generally confirmed in the present study, in one of our cases that was proved

* This work was done in part under a grant from the Proctor Fund for the Study of Chronic Disease.

to have an anterior infarction a $Q4$ was absent for about one week and then appeared a day or two before exitus.

The purpose of this study is to record the electrocardiographic findings in a group of 44 cases that have come to postmortem examination at the Peter Bent Brigham Hospital during this past year. An analysis was made of these data to see if the fore-mentioned criteria are reliable and to ascertain what limitations, if any, there may be in their application. In addition, a survey was made of the electrocardiograms in a routine group of 100 consecutive ambulatory cases of angina pectoris as seen in consultation practice. This was thought to be of some importance because although considerable data have already been accumulated concerning acute coronary thrombosis and myocardial infarction little has been published in relation to angina pectoris.

There is some difference in opinion concerning the exact technique in obtaining a precordial lead. Because the form of the ventricular complex varies considerably depending upon the part of the chest over which the electrode is placed, it has been suggested that numerous points over the precordium need to be explored to obtain a complete study. There has also been some question whether the indifferent electrode should be on the back of the chest or on the left leg. In order to simplify the technique and because Wilson[14] is of the opinion that nothing of importance will be lost thereby, we have kept the indifferent electrode on the left leg. Believing that a long series of electrocardiograms would be cumbersome and having adduced evidence that one precordial lead is insufficient, applications in all cases have been made with the right arm electrode first at the fourth left parasternal space and then in the region of the apex impulse. In most instances the new type of electrodes, using paste, was employed. We are aware of the fact that different electrocardiograms may result from slight changes in the position of the anterior electrode but the deductions that will be made will recognize this limitation.

Observations on 44 Autopsied Cases. There were 44 cases in this study that were examined postmortem in which tracings using both the conventional leads and Lead IV were obtained during life. Of these 17 died of coronary artery disease, 4 of hypertensive heart disease, 4 of valvular disease, 5 of pneumonia, and 14 of miscellaneous causes. In this way comparisons could be made between cases with and without disease of the coronary arteries and between cardiacs and non-cardiacs. We interpret Lead IV as "positive" (for myocardial infarction) if the Q-wave is absent* or if there are significant deviations of the RS–T segment. Lead IV is regarded

* Following the advice of Dr. F. N. Wilson, we do not regard as "positive" those instances in which there is a slight initial upward deflection of the Q–R–S in Lead IV, followed by a deep downward deflection, as this may occur normally, especially with the electrode at the apex.

as "questionably positive" if the *Q*-wave is present but measures 2 mm. or less in height. The term "abnormal Lead IV" is applied if the *T*-wave is upright and the *Q*-wave measures more than 2 mm. Finally Lead IV is termed "normal" if the *Q*-wave measures more than 2 mm. and the *T*-wave is inverted. The conventional leads are designated as "abnormal" if there is an abnormal form of ventricular complex with "coronary *T*-waves," deviation of the *RS–T* segment, low electromotive force, bundle-branch block or defective intraventricular conduction. Tracings with left ventricular preponderance, auricular fibrillation or flutter, or with a prominent *Q*-wave as an isolated finding are not regarded as abnormal for the purposes of this analysis.

As the tables show, there were 15 cases with "positive" Lead IV in at least one of the chest positions. Of the 11 patients "positive" at both the left sternal border and the apex, 9 showed anterior infarction. The tenth patient had chronic nephritis with terminal uremia and bundle-branch block; at autopsy there was no coronary occlusion or myocardial infarction, old or recent. The eleventh showed a tuberculous pericarditis at autopsy but no infarction. Of the 9 cases with anterior infarction at autopsy 6 showed "abnormal" conventional leads while 3 showed essentially normal conventional leads.

TABLE 1.—ANALYSIS OF DATA OF 15 AUTOPSIED CASES IN WHICH LEAD IV WAS POSITIVE.

Location.	Infarction.	Name.	Age.	Sex.	Clinical diagnosis.	Conventional leads.	Autopsy findings.
LSB and apex.	Present	N. B.	58	M	Cor. thromb.	AFVC (T_1)	Large ant. infarct.
		B. M.	57	M	Cor. thromb.	DIVC	Large ant. infarct.
		M. P.	69	M	Cor. thromb.	AFVC (T_1)	Large ant. infarct.
		L. M.	40	M	Cor. thromb.	AFVC (T_1)	Large ant. infarct.
		E. L.	59	M	Cor. thromb.	AFVC	Large ant. infarct.
		C. M.	79	F	Cor. thromb.	Complete ht. block; BBB	Large ant. infarct.
		A. M.	47	M	Cor. thromb.	LVP; inv. T_1 and T_2	Ant. infarct.
		Z. M.	62	F	Hypertensive ht. dis.	LVP; AF	Recent. ant. and healed post. infarct.
		V. S.	74	M	Coronary art. dis.	Delayed A–V conduct; VPB	Old and recent ant. infarcts.
LSB only	Absent	W. B.	41	M	Hypertens. ht. dis.; uremia	BBB (left)	Chr. nephritis; no pericarditis.
		P. M.	68	M	Pulmonary infarct.	LVP; $T_{1,2,3}$ flat	Tubere. pericarditis.
	Present	J. S.	75	M	Angina pectoris	LVP; AF; DIVC	Healed post. infarct.
		C. C.	63	F	Hypertensive ht. dis.	LVP; AF; $T_{1,2,3}$ inverted	Healed post. infarct.
		W. R.	55	M	Cor. thromb.	AF; auricular flutter	Large ant. infarct.
	Absent	O. G.	52	M	Syphilis	BBB (right)	Luetic aortitis with narrow coronary ostia.

There were 4 cases with absent *Q*-wave at the left sternal border only. Three of these showed infarction but in two the infarction, peculiarly enough, was located posteriorly and was of long standing. In the fourth case positive at the left sternal border only, who also had right bundle branch block, necropsy revealed luetic aortitis

TABLE 2.—ANALYSIS OF DATA OF 15 AUTOPSIED CASES IN WHICH LEAD IV WAS QUESTIONABLY POSITIVE.

Location.	Infarction.	Name.	Age.	Sex.	Clinical diagnosis.	Conventional leads.	Autopsy findings.
LSB and apex.	Present	F. N.	59	M	Cor. thromb.	DIVC; delayed A-V conduction	Recent ant. and healed post. infarct.
		J. S.	62	M	Cor. art. dis.	Low EMF; DIVC	Occlus. left and right cor. arts.; diffuse endocard. fibrosis.
		E. M.	61	F	Cor. thromb.	LVP	Old apical infarct; pul. embol.
	Absent	L. M.	58	F	Bronchopneu.	Delayed A-V conduc	Bronchopneu.
		A. R.	71	F	Rheum. ht. dis.	LVP	Bronchopneu.; pul. infarcts; mitral, aortic and tricuspid dis.
LSB only.	Present	G. S.	65	M	Cor. art. dis.	LVP; low EMF	Recent post. and healed ant. infarcts.*
		C. M.	58	M	Bronchopneu.	LVP	Occlusion descending branch left cor., no infarction; bronchopn.
		D. T.	78	F	Cerebral embolism	AF	Recent infarct left margin heart.
		O. J.	74	M	Angina pectoris	RVP	Old apical infarct.
	Absent	M. G.	79	F	Bronchopneu.	Comp. ht. bl.; DIVC	Bronchopneu.
		E. E.	33	F	Rheum. ht. dis.	AF; VPB	Mitral stenosis.
		J. E.	59	M	Polycythemia	LVP	Cerebr. thromb.; bronchopneu.
		L. L.	49	M	Uremia	Normal curves	Congen. polycystic kidneys.
Apex only.	Present	G. P.	44	M	Cor. thromb.	BBB (right)	Recent ant. and healed post. infarct.
	Absent	M. H.	59	F	Hypertensive ht. dis.	Low EMF	Death from congestive failure.

DIVC = Defective intraventricular conduction. BBB = Bundle branch block. AFVC = Abnormal form of ventricular complex. * = Fatal infarct may have occurred after EKG's were taken. RVP = Right ventricular preponderance. LVP = Left ventricular preponderance. AF = Auricular fibrillation. VPB = Ventricular premature beat.

TABLE 3.—ANALYSIS OF DATA OF 14 AUTOPSIED CASES IN WHICH LEAD IV WAS ABNORMAL OR NORMAL.

Infarction.	Name.	Age.	Sex.	Clinical diagnosis.	Conventional leads.	Autopsy findings.
Absent . . .	E. J.	55	M	Uremia	$T_{1,2,3}$ inverted	Chr. nephritis; bronchopneu.
	E. D.	59	M	Bleeding peptic ulcer	$T_{1,2,3}$ inverted	Death from exsanguination.
Present . .	M. H.	65	F	Cor. thromb.	AFVC (T_3)	Recent post. infarct.
Absent . . .	J. R.	38	M	Uremia	AFVC	Chr. nephr.; terminal pericard.
	D. C.	27	M	Rheumatic ht. dis.	BBB (right); AF	Mitral, aortic and tricuspid dis.
	S. K.	83	F	Hypertensive ht. dis.	Low EMF; delayed A-V conduction	Pulmonary embolism.
	C. R.	53	M	Rheumatic ht. dis.	AF; LVP	Bronchopneu.; mitral and aortic dis.
	N. A.	28	F	Uremia	LVP; $T_{1,2,3}$ inverted	Chr. nephritis; bronchopneu.; terminal pericarditis.
	J. S.	59	M	Carc. of cecum	Normal curves	Death from exsanguination.
	L. P.	75	F	Lobar pneu.	LVP	Lobar pneumonia.
	H. P.	66	M	Carc. of bladder	Auricular flutter	Carc. of bladder; acute fibrinous pericarditis.
	J. B.	71	M	Bronchopneu.	LVP	Bilat. confluent bronchopneu.
	E. C.	33	F	Pul. gangrene	Normal curves	Foreign body, r. lower bronchus.
	C. D.	26	M	Chr. nephr.; hypertensive ht. dis.	LVP	Chr. nephr.; pul. infarct.

with marked narrowing of the coronary ostia but there was no coronary occlusion or obvious myocardial infarction. Of the 4 cases in this group only 2 showed "abnormal" conventional leads, 1 showing defective intraventricular conduction and the other being the above-mentioned case of right bundle branch block. No cases were seen in which the apical lead was "positive" and the parasternal lead "normal."

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TABLE 4.—INTERPRETATION OF LEAD IV IN 44 AUTOPSIED CASES WITH AND WITHOUT MYOCARDIAL INFARCTION.

Interpretation of Lead IV.	Infarction present.		Infarction not present.	
1. Positive	12		3	
a. Positive at LSB and apex		9		2
b. Positive at LSB only		3		1
c. Positive at apex only		0		0
2. Questionably positive	8		7	
a. Questionably positive at LSB and apex		3		2
b. Questionably positive LSB only		4		4
c. Questionably positive at apex only		1		1
3. Abnormal	0		2	
4. Normal	1*		11	
Total	21		23	

* Changes in conventional leads typical of posterior infarction; verified at autopsy.

There were 15 cases in which Lead IV was regarded as "questionably positive." Seven showed infarction, 1 showed coronary occlusion without infarction, and 7 showed no infarction. This indicates that in about half the cases such questionable findings reflected the presence of gross disease of the ventricles and in the other half they did not. It did not matter whether these findings were present in the tracings obtained from the apex or left sternal border or whether they were accompanied by abnormal or essentially normal electrocardiograms in the conventional leads.

Lead IV was "abnormal" in 2 patients. One was a chronic nephritic who died in uremia. Autopsy showed a bronchopneumonia but no coronary artery disease or myocardial infarction. The other patient died of exsanguination from a bleeding peptic ulcer. Here again there was no infarction at autopsy. It is obvious therefore

LEGENDS FOR FIGURES 1, 2 AND 3.

FIG. 1.—Conventional three leads and fourth lead from the left sternal border and apex. *A*, Lead IV normal and autopsy showed a normal heart in a case dying of carcinoma of the cecum. *B*, Lead IV shows absent *Q*-waves in both positions diagnostic of an anterior infarction confirmed at autopsy. Conventional leads not distinctive. *C*, Lead IV shows absent *Q*-waves in both positions indicative of anterior infarction, confirmed at autopsy. Conventional leads also diagnostic of this lesion. *D*, Lead *IV* normal. Conventional leads indicative of posterior infarction, confirmed at autopsy.

FIG. 2.—*E*, Conventional leads show bundle branch block. Lead IV shows positive *T*-waves and slight initial upward movements of the *Q–R–S* complex. Autopsy showed an enlarged heart but no infarction. Patient died of uremia. *F*, Lead IV shows normal *Q*-waves but upright *T*-waves. Autopsy showed a normal heart. The patient died of uremia and bronchopneumonia. G, Lead IV shows small *Q*-waves (1.5 mm.). Autopsy showed recent anterior and old posterior infarction. *H*, Lead IV shows small *Q*-waves (1 and 2 mm.). Patient had a normal heart and died of bronchopneumonia, confirmed at autopsy.

FIG. 3.—Conventional three leads and fourth leads from the left sternal border and apex in 4 ambulatory cases of angina pectoris. *J* and *K* show absent *Q*-waves in Lead IV at both positions, whereas the conventional leads are essentially normal. *L* and *M* show absent *Q*-waves at the left sternal border only, the customary three-leads being not remarkable.

that an upright T-wave in Lead IV is of no value in the diagnosis of myocardial infarction. In fact we have seen a positive T_4 occur as a transient phenomenon during bronchopneumonia as have others, and as a permanent or transient finding under a variety of other circumstances such as mitral stenosis, uremia and hyperthyroidism.

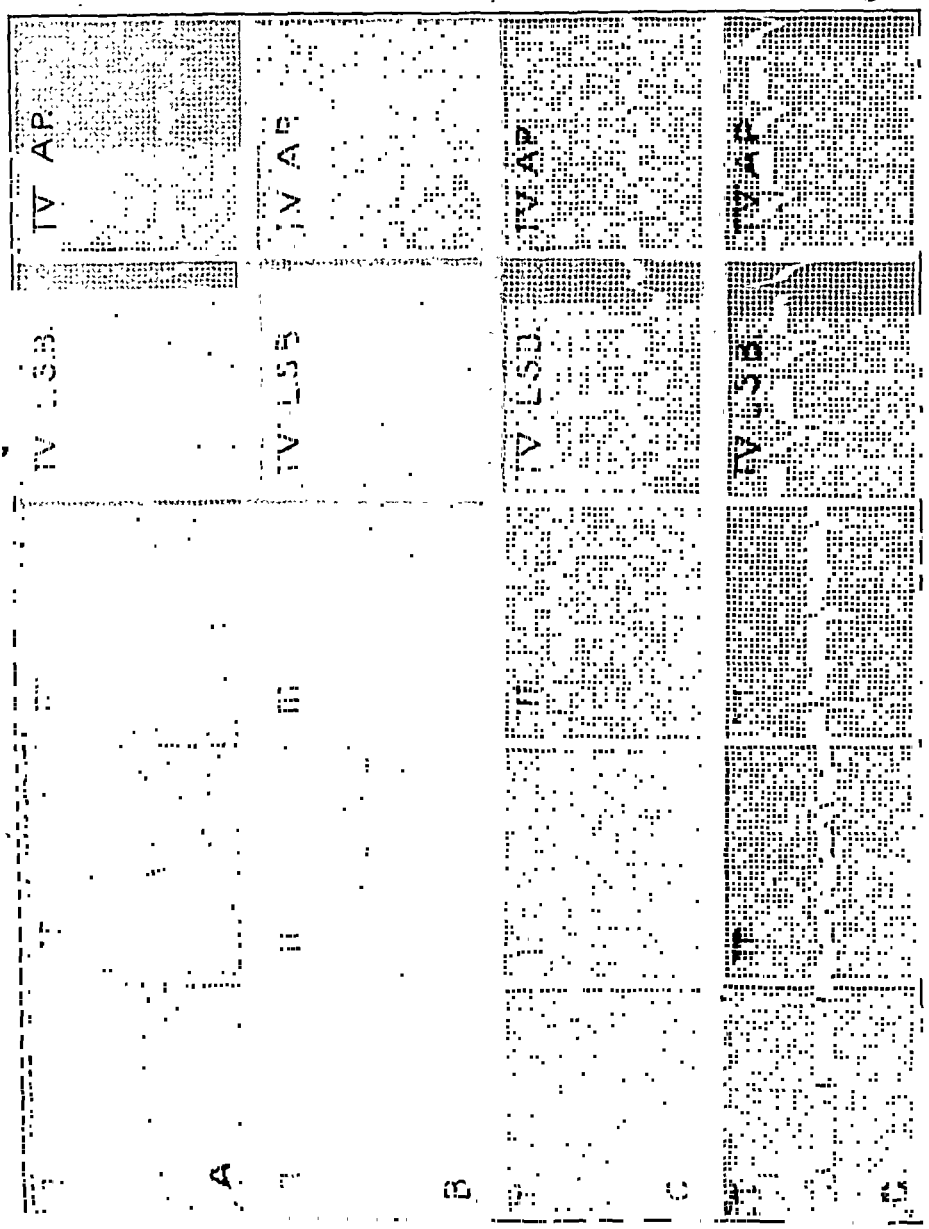


FIG. 1

In 12 cases Lead IV was "normal." In 1 of these changes occurred in the conventional leads typical of infarction of the posterior part of the heart. This was verified at autopsy. In the other 11 cases postmortem studies showed no infarction.

In reviewing these postmortem observations, we feel justified in concluding that the complete absence of a *Q*-wave in the apex lead invariably means infarction of the anterior portion of the ventricle

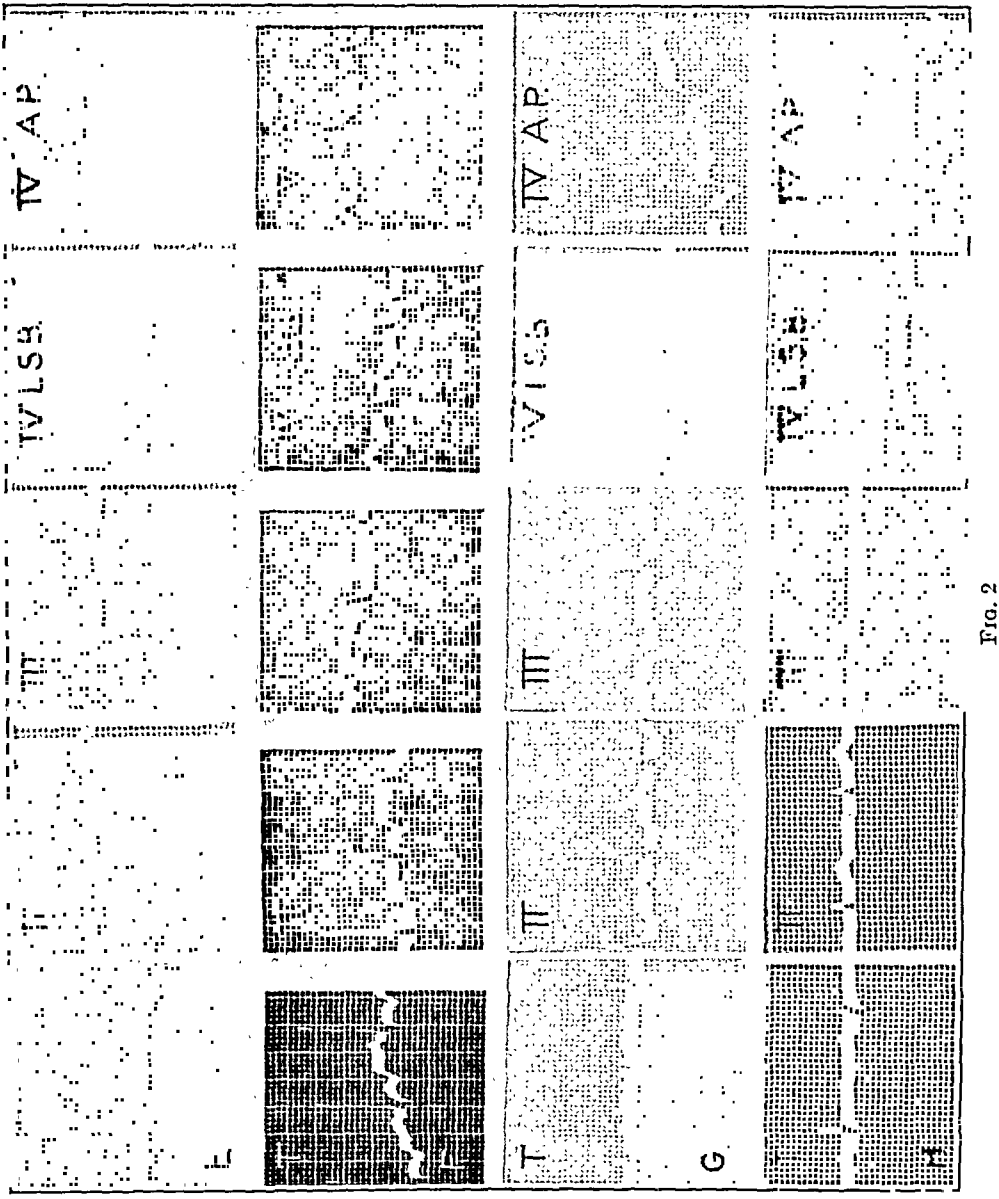


FIG. 2

except when bundle branch block or rarely when certain forms of pericarditis are present.

We have found in a series of 23 cases of bundle branch block that the *Q*-wave was absent in such an overwhelming proportion that it seems impossible to apply the same criteria in the diagnosis of

myocardial infarction when bundle branch block is present as when it is not present. When the Q_4 is absent in the lead taken from the left sternal border only, the infarction may be either anterior

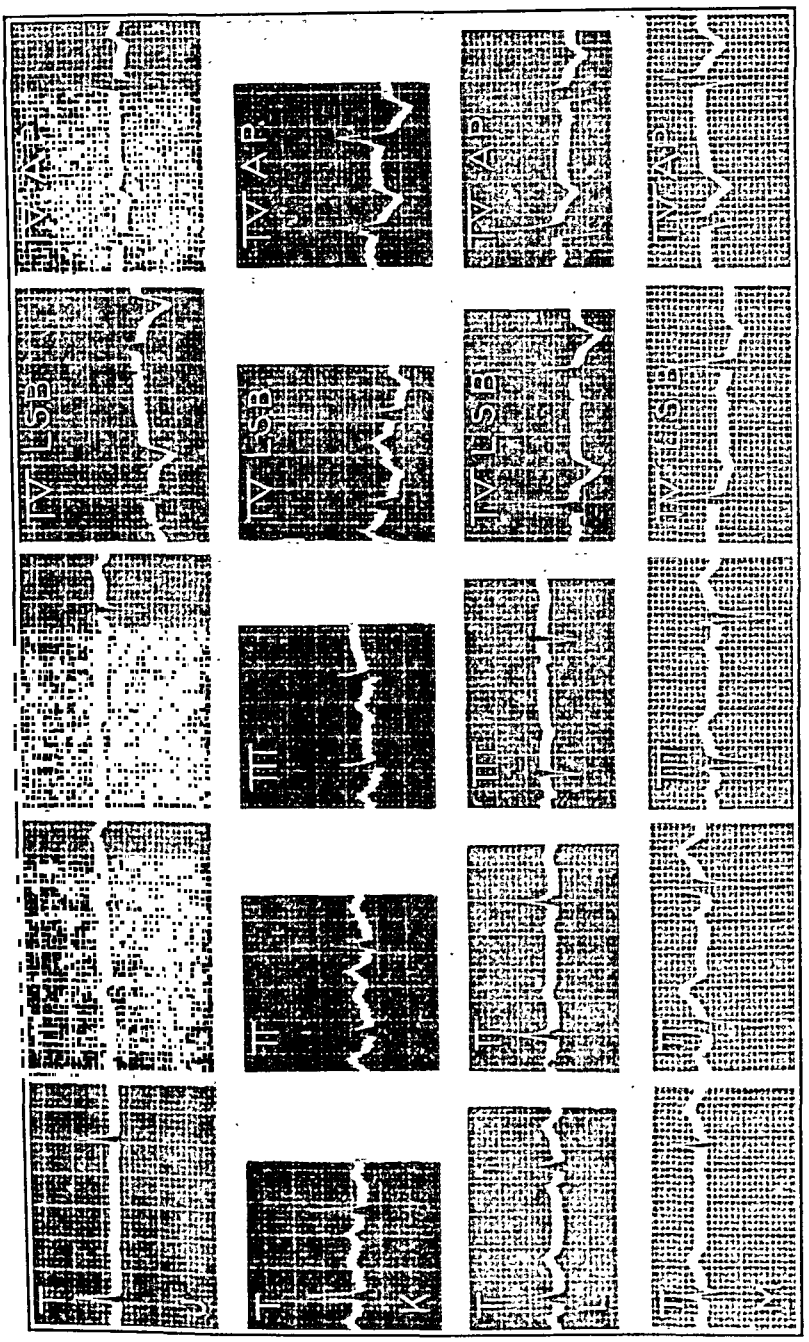


FIG. 3

or posterior. When normal curves are obtained in both applications in Lead IV infarction will not be present in the anterior but

may be present in the posterior part of the ventricle. When Q-waves of very small amplitude are found (2 mm. or less) there is an even chance that infarction will or will not be present. The finding of the presence of upright T-waves is of no help in the diagnosis of myocardial infarction. It is appreciated that this postmortem experience needs to be amplified considerably to ascertain further qualifications or limitations to these general views.

Observations on Lead IV in Angina Pectoris. Electrocardiographic observations were made on 100 consecutive ambulatory cases of angina pectoris. The customary three leads were obtained and in addition fourth leads both from the region of the apex and the fourth left parasternal space. All cases of known coronary thrombosis were excluded. The cases were selected only insofar as the diagnosis of angina pectoris was quite definite and the ordinary clinical history failed to reveal evidence of a previous attack of coronary thrombosis. In other words they correspond to the average case of angina that is ambulatory and has not had a severe major coronary attack. The same criteria as those mentioned above have been used for evaluating the electrocardiograms. In somewhat similar studies, but in which no sharp distinction was made between angina with and without coronary occlusion, Goldbloom[11] and Battro and Garcia del Rio[15] found many instances in which Lead IV was abnormal. Their criteria for abnormality include the presence of an upright T_4. This was shown above to be insufficient evidence of myocardial infarction.

In our 100 cases there were 44 in which the conventional three leads were regarded as essentially normal and Lead IV was also normal. There were 13 in which the conventional leads were "abnormal" and Lead IV was essentially normal. Most of these showed ventricular complexes in Leads II and III indicative of a lesion in the posterior part of the ventricle and therefore would not have been expected to display significant abnormalities in Lead IV. There were 9 cases, however, in which the conventional leads were "abnormal" in 5 of which Lead IV was "positive" and in 4 questionably so. The most important group in this part of the study comprised 11 cases in which the conventional leads were normal and Lead IV was "positive." Of these 11 cases, the positive findings were obtained at both the apex and left sternal border in 4 instances, at the left sternal border only in 6 and at the apex only in one. It follows therefore that 11% of the cases with angina pectoris showed positive evidence of myocardial infarction in Lead IV when similar evidence could not have been found in the routine 3 leads and in the ordinary clinical history.

Fourteen of these 100 cases showed changes in Lead IV that were regarded as "questionably positive" while the customary 3 leads were essentially normal. In 3 of these the abnormalities were found in both chest positions (Ap and LSB); in 9 at the LSB only and in

2 at the apex only. Inasmuch as it has been shown above that such questionable findings indicate myocardial infarction in about half of the cases, it can be inferred that in some of these 14 cases gross heart muscle scarring must have occurred.

Finally there were 9 instances with so-called "abnormal" Lead IV. This consists of an upright T_4. In 7 the customary 3 leads were normal and in 2 they were "abnormal." In view of the conclusion arrived at above that the isolated finding of an upright T_4 is not diagnostic of myocardial infarction this group cannot be regarded as valuable for the purpose of this study.

It is quite evident that electrocardiographic abnormalities in the ventricular complex, particularly the changes discussed in this paper, are the result of alterations in the heart muscle rather than in the coronary arteries. A narrowed or occluded coronary artery could only produce abnormalities in the electrocardiogram insofar as the structure or function of the heart muscle became impaired. For this reason myocardial infarction might be expected to show abnormal electrocardiograms. Here, however, in 100 cases of angina pectoris in which there is no evidence from the clinical history of any previous acute major episode that might have produced an infarct of the heart, there were 16 instances in which Lead IV gave definite evidence and 18 questionable evidence of myocardial infarction. In 11 of the former 16 cases the customary 3 leads were regarded as essentially normal. Inasmuch as the criteria upon which the electrocardiograms were interpreted have been proved to be extremely accurate by the study of the 44 autopsied cases reported above, we feel justified in inferring that the angina cases with a positive Lead IV have had myocardial infarction. This could be explained if we assume that some of the attacks of angina were actually instances of acute coronary thrombosis, although clinically they were not severe enough to be regarded as such or require the patient to go to bed. Another possible explanation is that myocardial infarction takes place in those suffering from angina pectoris as a gradual process without any acute dramatic episode. From the pathologic point of view the latter is not uncommon, for infarcts of the ventricular musculature are not infrequently seen when on ordinary examination the coronary vessels fail to show any thrombosis or occlusion. Finally, since the work of Robb, Easby and Hiss[16,17] it seems very likely that many small infarcts of the heart muscle occur, capable of producing distinct electrocardiographic abnormalities which are the result of the occlusion of finer coronary arterioles that could easily be overlooked on the ordinary postmortem examination. At any rate there can be no doubt that patients with definite angina pectoris who give none of the customary clinical evidence in the past history of an acute coronary thrombosis, frequently manifest electrocardiographic changes which serve as indisputable evidence of myocardial infarction and that

such evidence may be present in Lead IV and not in the ordinary 3 leads.

Summary. 1. Electrocardiographic study was made of 44 patients who were subsequently examined postmortem. The customary 3 leads were taken and in addition fourth leads with the anterior electrode at the fourth left sternal border and at the apex and with the indifferent electrode on the left leg.

2. In 12 instances in which the Q-wave was absent in Lead IV either at the left sternal border or at the apex, infarction of the ventricle was found. Two cases with bundle branch block and 1 of tuberculous pericarditis with absent Q_4 showed no infarction.

3. There were 15 cases with small Q_4 (2 mm. or less), about half of which had infarction and the other half did not.

4. Upright T-waves in Lead IV were found when no infarction was present and in fact where there was no significant heart disease.

5. In 11 cases in which the heart was normal and in 1 with posterior infarction Lead IV was normal.

6. Evidence is presented to show that myocardial infarction is not uncommon in angina pectoris when there is no clinical evidence of a previous coronary thrombosis. Sixteen of 100 cases showed an absent Q_4 and in 11 of these the customary 3 leads were essentially normal.

7. Apart from the changes in Lead IV which occur during the acute phases of coronary thrombosis, we believe that the absence of Q_4 is very helpful in the diagnosis of a previous myocardial infarction, except when bundle branch block is present.

8. Lead IV is indispensable in the proper diagnosis of certain cases of heart-muscle disease.

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MITRAL VALVE DISEASE.

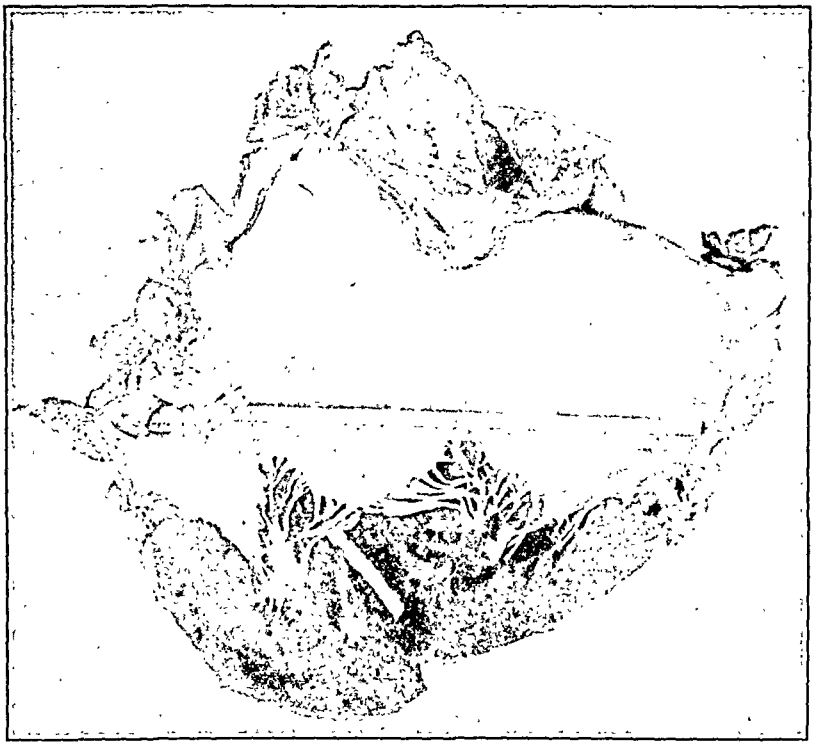
Pathologic Report.

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and
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Thirty years ago we were accustomed to think of rheumatic endocarditis of the mitral valve in terms of mitral regurgitation (insufficiency) or of mitral stenosis. Today, in considerable part because of the mass experience with heart disease provided by the war, modern cardiology practically ignores organic mitral regurgitation as a definite disease condition, and accepts all symptoms and signs of mitral disease as evidence of mitral stenosis. Cabot[1] indeed, describing those physical signs which formerly he accepted as proof of mitral regurgitation, now designates these same signs as indicating an early stage of mitral stenosis.

Lewis,[2] who more than any other authority, is responsible for our present concept, holds that mitral regurgitation is not physically disabling, and that "the presence or absence of systolic murmurs is of no value in estimating . . . capacity for work," while an editorial writer[3] in answer to a question, states that "mitral regurgitation is not a clinical or an anatomic entity." The general viewpoint in the matter is perhaps expressed in the opinion of a well known writer,[4] that "it is better to speak generally of mitral involvement, the high grades of which always mean mitral stenosis," and the belief of another writer[5] that "uncomplicated (primary) mitral insufficiency should be classed among the comparatively infrequent valve lesions."

Is it indeed true that organic mitral regurgitation is uncommon, that high grades of mitral disease always mean mitral stenosis, or that mitral regurgitation is a minor defect, never causing serious physical disability? While I had never accepted the modern concept of mitral disease, my interest in attempting to get more information on the subject was stimulated by having the care of a patient whose case history and pathologic report are given later—who died as the result of an uncomplicated rheumatic endocarditis of the mitral valve, with regurgitation and without stenosis.



Photograph of the heart (Case A–34–601). The ruler is placed across the mitral valve ring and measures 15 cm. in length.

In making this study, it was first necessary to obtain standards of normal valve measurements. For this purpose the protocols of 300 normal and pathologic hearts, weighing from 160 to 900 gm. were examined, and 100 hearts weighing from 190 to 690 gm. were averaged as to valve measures.

	Tricuspid valve.	Pulmonic valve.	Mitral valve.	Aortic valve.
Average for above 100 hearts	11.87 cm.	7.40 cm.	9.29 cm.	7.15 cm.
Average of 67 hearts in which the ratio of valve measures was acceptable . . .	11.77 cm.	7.35 cm.	9.40 cm.	7.01 cm.
Ratios of valve circumference to that of aortic valve	$1\frac{2}{3}$	$1\frac{1}{20}$	$1\frac{1}{3}$	1.0

It seemed that the upper and lower acceptable limits for the four valves were:

Tricuspid valve	13.0 to 10.0 cm.
Pulmonic valve	8.0 to 6.0 cm.
Mitral valve	11.0 to 8.0 cm.
Aortic valve	8.0 to 6.0 cm.

Norris[6] is quoted as giving the average measure of the mitral valve at 11.037 cm. in men and 9.268 cm. in women. On the other hand, Herrmann[7] states that the normal mitral ring measures 10 cm., the tricuspid 12 cm., and that as long as the circumference of the mitral valve is not less than 7.5 cm. with an area of not less than 450 sq. mm., or the tricuspid is not less than 8 cm. in circumference in any part with an area for the orifice of 500 sq. mm. or more in an adult, there is practically no significant obstruction.

So far as the mitral valve is concerned, the observation of Herrmann corresponds with my experience that a valve 7.5 cm. in circumference may not be stenosed. The observation as to the tricuspid valve in Herrmann's report cannot be confirmed or refuted by the small number of measures that I collected, since tricuspid stenosis is uncommon in adults. In any event, such standards are subject to the personal bias of the observer and to his acceptance or rejection arbitrarily, for inclusion in his averages, of examples larger or smaller than ordinary; since in the averages collected by me, no tricuspid measures larger than 14.4 nor smaller than 10 cm., and no mitral measures above 11 nor below 7.5 cm. were included, obviously the result was "weighted" to this extent from the start.

It may be argued that the proposition here presented concerns merely the stretching of the mitral ring—in other words a relative mitral regurgitation. To this extent, I am quite ready to agree with this argument: I am inclined to believe that most patients who die of uncomplicated organic mitral regurgitation have before death a dilatation of the mitral ring, just as they may also have a dilatation of the tricuspid ring.

The mere fact that, as the result of the final breaking down of the cardiac reserve, dilatation of a valve ring may occur, cannot explain away an actual chronic inflammation of the valve present at autopsy; indeed, the stretching of diseased mitral valve segments and ring, in a patient whose rheumatic history goes back many years and who is known to have had heart disease for many years, would seem to be proof that there was no vestige of stenosis present, and that mitral disease of very long standing does not necessarily produce stenosis of the valve.

Every single case record included in this series showed at autopsy definite evidence of a chronic inflammatory non-atheromatous process, which had deformed the mitral leaflets to a greater or less extent, and in which a pathologic diagnosis of chronic endocarditis had been made.

To many pathologists, a cicatrized mitral ring, or a "fish-mouth" or "button-hole" mitral orifice, while representing a very high grade of stenosis, also indicates a definite insufficiency of the valve, in that such a valve is considered incapable of complete closure. That curling or narrowing of the valve segments, shortening or thickening of the chordæ tendineæ are all evidence in varying degrees of insufficiency of the mitral valve, seems to be universally accepted. In this analysis of cases of mitral endocarditis, the above criteria have been followed.

The valve measurements in the protocols studied, were made with a flexible celluloid ruler; in general these measures indicate the size of the valve ring, but where the valve orifice is smaller than the ring, the size of the opening is indicated either by figures or by finger measurements. Where two measures are given, I have used the smaller—which is to say the size of the valve orifice—in the classification of cases.

Except for the valve measures cited by Tice and Herrmann already mentioned, I know of no book on anatomy, pathology, or heart disease that gives any indication as to the normal or abnormal valve measures. Apparently each pathologist makes his own diagnosis as to the presence or absence of stenosis, without any hard and fast rule, or else he goes out and makes his own set of standards, as was done here.

Of 150 cases of mitral endocarditis, there were in all only 11 cases here listed as without stenosis, in which the pathologist noted as his opinion that there was stenosis.

One interesting point brought out in the study of the size of the mitral valve, and which would seem to be contrary to the observation of Norris, was that the mitral valve averages showed relatively little variation for hearts of different sizes. One heart, not included in the total of 100, of 160 gm., in a young woman, had a measure of 8 cm.; 11 hearts of 190 to 245 gm. averaged 8.52 cm. Leaving these out of consideration, in the 89 hearts ranging from 250 to 690 gm. weight, the average for the smallest group showed mitral valves of 9.22 cm. and for the largest group 9.61 cm., with two groups, intermediate in weight, each averaging 9.73 cm.

In the following analysis of cases of mitral endocarditis, the cases were divided into those with a mitral valve measuring 8 cm. or more, and those measuring less than 8 cm. Each of these groups was again subdivided. Those cases where the mitral measure was less than 8 cm., could be classed as either mitral stenosis, or as mitral stenosis and regurgitation; those cases showing a circumference of 8 cm. or more at the mitral valve were further grouped as mitral endocarditis without stenosis or as mitral regurgitation. While these groupings were largely based upon the pathologic findings in regard to the mitral valves the chordæ tendineæ and the papillary muscles, some weight was given to the relative size of

the ventricles and to the electrocardiogram reports when available. Since many of these patients entered the hospital moribund or with a terminal condition other than of cardiac origin, electrocardiograph studies were made only upon about one-third of the patients. Quite naturally, mitral lesions were often only a part of the cardiac pathology in many cases, so that help in the analysis of a particular case which might have been furnished by the electrocardiogram was often cancelled by a lesion of some other valve or by a pericarditis.

While it is relatively easy, in cases of mitral endocarditis without stenosis to recognize the presence of pure mitral regurgitation, the differentiation of pure mitral stenosis from cases also showing regurgitation is almost impossible pathologically. Self-evidently, mitral stenosis is readily excluded in a valve measuring 10 to 15 cm., but to say whether a valve of 3 to 6 cm. is or is not competent, is difficult to determine by the pathologic methods commonly in use, although the article in Oxford Medicine previously referred to, describes a method of opening the heart from above, whereby the physiologic competence of the valves may be demonstrated. Perhaps the use of such a procedure in a large number of autopsies would increase our knowledge. White,[8] referring to "pure" mitral stenosis, speaks of it as possible "when the valve cusps are fused, giving rise to a mitral stenosis without sufficient fibrosis or thickening of the cusp extremities or shortening of the chordæ tendineæ to allow regurgitation."

While there seems to be no certainty of identification of cases of pure mitral stenosis, I have arbitrarily so listed 11 cases showing a high-grade stenosis without marked cardiac enlargement.

In all, 150 cases showing endocarditis of the mitral valve at autopsy were studied in this series; 76 of these mitral valves were not stenosed, while 74 mitral valves showed stenosis with or without regurgitation; 35 cases were to be classed apparently as mitral regurgitation. Contrary to the standard for mitral stenosis previously stated, I have included with those showing no stenosis, 3 hearts in which the mitral measures were 7.5, 7.7, and 7.8 cm. In none of these 3 did the pathologist note stenosis, 2 of the patients were under 14 years, and each of these hearts had all of the valves small and in normal ratio.

Table 1 shows the numbers in each classification, the murmurs found, and the electrocardiogram reports. Although the murmurs give little direct information, one may speculate in regard to them as follows: (1) that in some cases, the presystolic murmur found alone may have actually been systolic in time; (2) that doubtless a thick edged valve, even if not stenosed, might cause vibrations in diastole resulting in a murmur, and that a diastolic murmur may also occur where the ring is stretched above a mitral valve of normal size; (3) that where there is a calcified ring and only a systolic murmur, there

TABLE 1.—DATA IN 150 CASES WITH VALVULAR DEFECTS.

Pathologic diagnoses.	Murmurs.									Lesions.			Electrocardiogram.				
	Number of cases.	Systolic murmur only.	Diastolic murmur only.	Presystolic murmur only.	Systolic and diastolic murmurs (apex).	Systolic and presystolic murmurs.	Systolic, diastolic and presystolic murmurs.	Diastolic and presystolic murmurs.	No murmurs heard.	Endocarditis of other valves only.	Pericardial adhesions only.	Pericarditis and other lesions.	Left preponderance.	Right preponderance.	Normal axis.	A-V or branch block or fibrillation.	No record.
Mitral stenosis—pure	9	2	0	1	2	0	0	0	4	..	..	..	0	1	2	0	6
and other lesions	2	1	0	0	1	0	0	0	0	2	0	0	0	0	0	0	2
Mitral stenosis and regurgitation, pure	35	10	0	0	10	0	0	2	13	..	..	..	2	5	1	2	25
and other lesions	28	6	0	0	12	4	2	0	4	23	1	4	2	6	1	2	17
Mitral endocarditis without stenosis, pure	18	3	1	2	2	1	2	0	7	..	..	..	1	2	1	0	14
and other lesions	23	9	1	0	7	2	0	0	4	19	2	2	5	0	2	1	15
Mitral regurgitation, pure	14	9	0	0	1	0	1	0	3	..	..	..	2	0	1	0	11
and other lesions	21	8	0	0	6	1	0	0	6	11	6	4	4	1	5	0	11
Totals	150	48	2	3	41	8	5	2	41	55	9	10	16	15	13	5	101

is probably a constant flow of blood from the auricle into the ventricle, the absence of a diastolic murmur tending to indicate an absence of obstruction. It is worthy of note that in almost one-half of the cases in which any murmur at all was heard, the only murmur present was systolic.

TABLE 2.—CLINICAL DIAGNOSIS.

Mitral stenosis and regurgitation	39	Syphilitic heart disease	1
Mitral stenosis	25	Cardiac hypertrophy	1
Rheumatic heart disease	22	Acute dilatation of heart	1
Arteriosclerotic heart disease	16	Coronary disease	1
Chronic myocarditis	9	Portal cirrhosis	1
Auricular fibrillation	7	Cerebral hemorrhage	1
Hypertensive heart disease	7	Carcinomatosis	2
Mitral regurgitation	4	Hyperthyroidism	1
Cardiac decompensation	4	Chronic cholecystitis	1
Acute endocarditis	2	General peritonitis	1
Aortic regurgitation	1	Pulmonary tuberculosis	1
Aortic stenosis and regurgitation	1	Fracture of skull	1
		Total cases	150

From the purely pathologic aspect, then, we can say that about one-half of all cases of mitral valve disease show no stenosis of the valve, while actual insufficiency of the mitral is present in between one-quarter and one-half;[9] that mitral stenosis either does not exist by itself or, if it does, that there is no certainty of its recognition. What, then, about the clinical side of the picture? Are all high

grades of "mitral involvement" always stenotic, as stated by one of the authorities quoted? By no means. Among mitral endocarditis cases without other valve involvement or pericarditis, there are as many very large hearts to be found without stenosis or with regurgitation alone at the mitral valve, as there are very large hearts with a high-grade stenosis. In fact, all the evidence seems to indicate that mitral stenosis by itself is not a cause of much cardiac hypertrophy. From the physiologic point of view, it is difficult to see how uncomplicated mitral stenosis can cause hypertrophy of the left ventricle—often the left ventricle is atrophied in such cases—and without left ventricular hypertrophy the heart does not tend to be very large.

Can uncomplicated mitral endocarditis without stenosis ever be, of itself, a cause of death? In spite of modern cardiology, it would seem so. In this series of 150 cases, there were 32 cases of mitral valve endocarditis without stenosis, uncomplicated by lesions of other valves or by pericarditis. For 25 of these deaths, acute or chronic diseases other than chronic mitral endocarditis could be blamed in part or entirely. Of the remaining 7 cases, 1—that of a woman of 65 with possible arteriosclerotic heart disease—may be omitted as doubtful, although the mitral valve was incompetent, the wall of the left ventricle was 2.2 cm. in thickness, and I believe that she died of mitral regurgitation. The other 6 patients, all with histories of old rheumatic heart disease, and the oldest of them only 50 years, would seem to have died of no cause other than secondary to a pure mitral regurgitation.

In regard to this, it is interesting to note that experimental physiology does not seem to agree with modern cardiology in comparing the relative importance of stenosis and regurgitation at the mitral valve. I quote from Oxford Medicine:[10] "Quite contrary to our traditional clinical conceptions, mitral stenosis in artificial circulation schemata and that produced experimentally, seems to add a load that is more easily borne, even with very high-grade lesions, than is the burden of mitral insufficiency."

It would seem that we are now placing too much emphasis on the importance of a narrowing of the mitral ring, too little on the rôle that insufficiency of the valve plays, in mitral endocarditis.

Case History. J. H. P., aged 50, married, traveling salesman, under observation in hospital 9 weeks. Had been in good health until 21 years ago, when a life insurance examination showed "some sort of heart trouble" due, he was told, to acute rheumatic fever which he had when 15. Worked until 3 years ago, when he began to have attacks of dyspnea, chest pain and edema of ankles; was then in hospital for the first time, staying 5 weeks. Has been using digitalis at times. Complaint now as in previous admission, with addition of "pounding of the heart" and oliguria.

Physical Examination. Orthopnea marked. Heaving of entire precordium. Heart action irregular. Lungs reported as negative. *Heart:* Impulse heaving and tumultuous, maximum in 6th left space, with occasional systolic thrill at apex. Loud systolic murmur at apex, largely replacing

first sound, transmitted all over precordium to axilla and to back. Variable pulse deficit. Abdomen negative. Liver not enlarged or tender. No edema of extremities. Blood pressure 120/95. On admission, Roentgen ray showed a rheumatic deformity of heart with enlargement both to the right and to the left and congestive changes of both lung fields. Later fluoroscopy noted a marked posterior bulging of the heart, especially of right auricle. Urine on admission showed an apparent acute nephritis which cleared up. Later blood pressures 155/90; 155/95; 130/70; 145/100; 140/80. Mosenthal and blood examination negative; non-protein nitrogen at first high, then normal. Electrocardiogram showed slight left predominance, auricular fibrillation, and, in the three positions, a well marked change of axis of the heart of +24 degrees.

One week before death, systolic expansile pulsation of the liver was noted, without positive venous pulse or separate murmur in tricuspid area. At all times there was a loud systolic murmur and at no time was a murmur heard in diastole. After early improvement, patient failed and died on the 64th day.

Pathologic Report. At autopsy (Dr. J. A. Reidy, 5½ hours after death) the patient showed moderate edema of both legs to the knees and a small amount of clear fluid in either chest cavity.

The heart is moderately hypertrophied and markedly dilated, and weighs 700 gm. The measurements were as follows: tricuspid valve 15 cm.; pulmonic valve 9.4 cm.; mitral valve 16 cm.; aortic valve 7.6 cm.; wall of left ventricle 2.4 cm.; wall of right ventricle 1 cm. The hypertrophy is most marked in the right ventricle, the wall of which is 1 cm. thick. Both auricles are dilated, especially the left, which contains 500 cc. of clotted blood with no evidence of antemortem mural thrombosis. The auricular endocardium is generally thickened and whitish with a small corrugated area above the posterior leaf of the mitral valve. The tricuspid, pulmonary and aortic valves are grossly negative. The mitral orifice readily admits four fingers and, on opening, the leaves, especially the posterior, are found markedly thickened, rolled and shortened, but not in the least inter-adherent, so that no stenosis is produced. The chordæ tendineæ are thickened and slightly shortened. The coronaries arise anomalously from a single aortic sinus, and present many small intimal atheromatous patches. The foramen ovale is closed.

The lungs present marked chronic passive congestion with a few antemortem thrombi in veins of the right upper lobe, and a terminal bronchopneumonia. The branches of the pulmonary artery are uniformly thickened and show scattered atheromatous patches.

The remaining viscera show only the changes of marked chronic passive congestion save the right kidney, which contains a small, fairly recent cortical infarct 1 cm. in diameter. No apparent source of embolus causing this infarct is apparent.

Microscopically the heart muscle shows slight lymphocytic infiltration and a few small areas of scarring, but no Aschoff bodies or other evidence of an active myocarditis.

Summary. 1. One-half of all cases of rheumatic endocarditis of the mitral valve show no stenosis of this valve at autopsy, even in cases known to have been of many years' duration.

2. Pure mitral stenosis is rarely found at autopsy, it cannot be recognized with certainty even when present, and modern physiologic study would seem to suggest that the clinical importance of mitral stenosis is at present too much emphasized.

3. Pure mitral regurgitation is not uncommon, occurring in one-fifth to one-half of all cases of rheumatic endocarditis of this valve; it can of itself cause death, and it is believed that regurgitation is entitled to a more prominent place than it now holds in the study of mitral disease.

4. Clinical and pathologic analyses were made of 150 cases of mitral endocarditis, after a preliminary study of about 300 hearts to establish standards for comparison.

5. One clinical case history, with autopsy findings, is presented.

I wish to express my indebtedness to Dr. Frederic Parker, Jr., and to Dr. George K. Mallory for much help and encouragement, as well as to Dr. James H. Peers and to Dr. Louis F. Curran.

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THE EFFECT OF CALCIUM INJECTIONS ON THE HUMAN HEART.

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The effect of calcium on the animal heart has been established beyond doubt by numerous physiologic and pharmacologic experiments. Observations on humans, however, have so far given scanty evidence of any such effect. In a recent paper, I[1] have presented a critical review of the literature on that subject. Clinical reports dealing with oral calcium administration are not at all reliable. Observations on the cardiac effect of intravenous injections of calcium are more convincing, yet lack graphic proof. To furnish such proof is the object of the present study.

Method. Twenty-six adult individuals, 21 males and 5 females, were available for this investigation. All were apparently free from cardiovascular disease. The three standard leads of the electrocardiogram were

taken first. Lead II was then taken again, and, with the patient remaining in the electrocardiographic circuit, 10 cc. of a 20% solution of calcium gluconate* were injected into the left cubital vein. The average duration of each injection was 15 seconds. Such rapidity of injection was found necessary for maximal electrocardiographic effect. The electrocardiographic records were taken continuously before, during, and for several minutes after the injection. The duration of the injection was marked on each tracing.

To eliminate factors other than the calcium salt as the possible causes of the electrocardiographic changes found in this work, 18 individuals free from cardiovascular disease were selected as controls. The same technique was employed, only, instead of calcium gluconate, 10 cc. of physiologic sodium chlorid solution were injected. Electrocardiographic records were also taken before, during, and after these injections.

Results. The effects of the calcium injection on the configuration of the waves of the electrocardiogram are best illustrated by a typical case (Case 16). Here the injection itself consumes 12 seconds. Four seconds later, a progressive change in the *T* waves appears. They become flatter and flatter, and, 10 seconds after the termination of the injection, they are partly inverted in a few beats. Until 25 seconds after the end of the injection, the *T* waves remain flat. Then their height begins to increase, and, 50 seconds after the termination of the injection, they have practically reached their initial height of 3 millivolts and their original configuration. For about 25 seconds, no further change in the form of the waves presents itself. In the meantime, however, marked bradycardia has made its appearance. It will be discussed later. Simultaneously with it, a new change in the form of the electrocardiogram appears. This time, the *P* waves diminish in height; 75 seconds after the termination of the injection, they are partially inverted in two cardiac cycles. For about 20 seconds, they remain flat, then they very slowly regain their original height and contour.

At no time during the whole experiment do we note any change whatsoever in the form and duration of the *Q–R–S* complexes or in the duration of the *P–R* interval.

The changes just described represent the effect of the calcium injection on the form of the electrocardiogram in the typical case. In some instances, the changes were less marked, especially when the injection had been given more slowly. In other cases, however, there was frank inversion of the *T* and *P* waves. Figure 1 shows 3 examples of such changes.

Besides, the calcium injections had a remarkable effect upon the heart rate. They produced bradycardia. If we return to the typical case discussed before, we find a heart rate of 83 before the injection, while the standard leads are being taken. During the injection the rate rises, and immediately after, it is 100. We must bear in mind that the patient has just had an intravenous injection, with

* I am indebted to the Sandoz Company for supplying the ampuls of calcium gluconate used in this study.

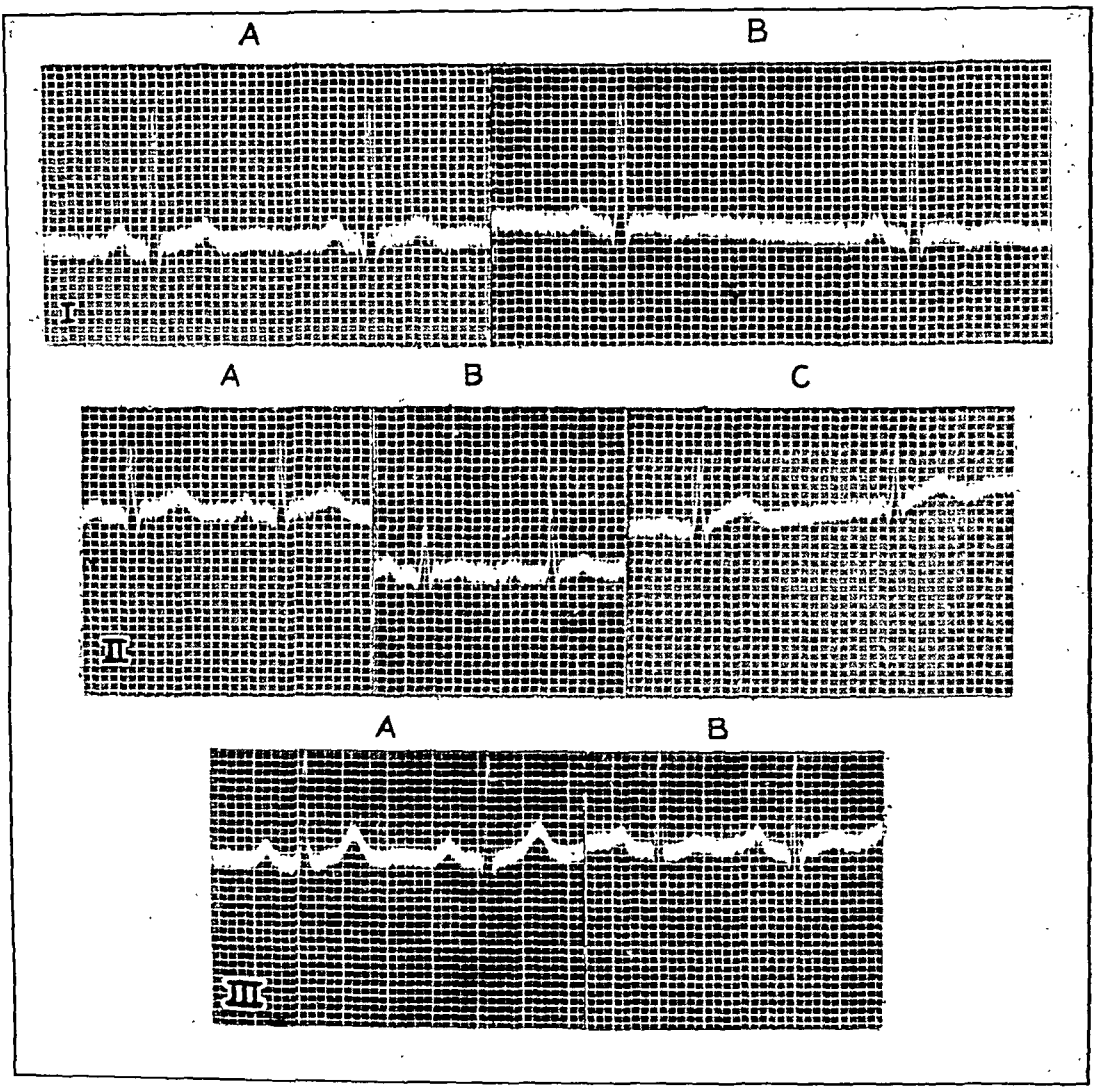


FIG. 1.—Three examples of electrocardiographic changes produced by calcium injections.

Case 1.—*A*, before injection. *B*, 27 seconds after termination of injection. Note bradycardia and inversion of *T* waves.

Case 2.—*A*, before injection. *B*, 16 seconds after termination of injection. Note tachycardia and flattening of *T* waves. *C*, 53 seconds after termination of injection; note inversion of *P* wave.

Case 3.—*A*, before injection. *B*, 25 seconds after termination of injection. Note flattening of *T* waves.

the anxiety which frequently accompanies such an experience. After the injection is completed, the heart rate at first rises still further. Twelve seconds later, at about the same time that the patient has a strong sensation of heat pervading his whole body, the heart rate reaches a maximum of 115 beats per minute. This tachycardia* lasts for 16 seconds, then the heart begins to slow down. One minute after the termination of the injection, it has fallen to 57. Soon after that, it reaches the record low of 51. Bradycardia then persists, lasting longer than the patient can be kept under continuous electrocardiographic observation. (According to Billigheimer[2], it lasts about 30 minutes.)

Bradycardia as well as changes in the *P* and *T* waves are the principal effects of calcium in the typical case. Tables 1 and 2 summarize the frequency of each of these three effects. The tables show the *T* wave change to be the most constant of the three. It appears in 92% of the cases. Bradycardia is next in frequency, with 67%. *P* wave changes are the least constant, being present only in 54% of the cases.

Beside these three principal signs, a number of other interesting phenomena were occasionally observed:

TABLE 1.—EFFECT OF CALCIUM INJECTION ON *P* AND *T* WAVES—26 CASES.

	Cases.	%.
T wave changes:		
T waves flattened	18	69
T waves semi-inverted	4	15
T waves frankly inverted	2	8
No *T* wave changes	2	8
P wave changes:		
P waves flattened	12	46
P waves inverted	2	8
No *P* wave changes	12	46

TABLE 2.—EFFECT OF CALCIUM INJECTION ON HEART RATE—24 CASES.*

	Cases.	%.
Bradycardia	16	67
No change in heart rate	8	33

* Two cases could not be included in this series as their tracings were not long enough to show the full effect of calcium on the heart rate.

1. Ventricular premature beats were noted in 2 out of 26 cases.

2. Sinus arrhythmia of varying degree was frequently seen. Where sinus arrhythmia was present before, the injection markedly intensified it.

3. Finally, another effect must be recorded, which fortunately occurred only in 2 cases: sinus arrest. In 1 case, during the period of bradycardia, there was no cardiac contraction for 4 seconds. The patient experienced only slight discomfort. In another case, however, the heart rate first slowed to 23 beats per minute, then,

* This tachycardia was not at all a constant finding. It was usually observed in nervous, apprehensive individuals, and may well be explained as a nervous reaction to the heat sensation rather than as a direct effect of calcium.

40 seconds after the end of the injection, cardiac standstill occurred. It was accompanied by a brief attack of syncope which necessitated termination of the electrocardiographic observation. No further ill effects were noted in this patient. Yet the experience was alarming enough to limit the choice of cases from then on to rather vigorous individuals, as both cases of sinus arrest had been of somewhat frail physique. Incidentally, it may be said that without that limitation the percentage of frank *T* wave inversions probably would have been greater.

The 18 injections of physiologic salt solution, on the other hand, yielded entirely negative results. In none of these controls had the injection any effect whatsoever on the heart rate or on the form and duration of the electrocardiographic complexes.

Comment. In this study, for the first time, experimental proof has been supplied of the effect of calcium on the normal human heart. Calcium has a direct effect upon the myocardium of the auricles and ventricles as shown by the changes in the *P* and *T* waves. This effect upon the myocardium is immediate as proved by the early appearance of the *T* wave changes which are usually demonstrable 4 seconds after the termination of the injection. There is, besides, an effect upon the nervous control of the heart, shown principally by the bradycardia; but this second effect is not as immediate.

No experiments of this type were ever done on human subjects before with the exception of a single case reported by Segall and White.[3] These authors gave their patient an intravenous injection of 75 cc. of a 2% solution of calcium chlorid, at the rate of 5 cc. per minute. Although marked diuresis resulted, electrocardiograms taken just before and 5 minutes after the injection showed no difference whatsoever. In the light of my experience, this failure is not at all astonishing. By the time these authors took the second tracing, the *T* wave changes, if present at all, had already disappeared! Yet even if Segall and White had taken continuous records, they might not have obtained any electrocardiographic changes because they used a weak solution and injected it slowly. To obtain effects, I had to use a 20% solution of calcium gluconate and had to inject 10 cc. in 15 seconds or less. Half of my failures to produce bradycardia or *T* wave changes were attributable to an unusually slow injection, as for instance in 1 case where the injection consumed 58 seconds.

Viewed from the standpoint of the practitioner, these results certainly support the often stressed necessity of injecting calcium slowly. Intravenous calcium injections, they prove, are quite harmless when given very slowly and in proper amounts, yet are potentially dangerous to the heart when administered rapidly.

Furthermore, the question of therapeutic application remains to be considered. The present study was not devoted to an inves-

tigation of the therapeutic problem, and only little can be said about it at this time. Leaving aside the mild diuretic effect of calcium, two possibilities of utilizing the direct cardiac effect seem open. First, the effect on the heart rate may be used in the treatment of the tachycardias with regular rhythm. Wolffe and Bellett[4] were the first to employ calcium for that purpose. In 3 cases, they were able to terminate attacks of paroxysmal tachycardia by intravenous injection of calcium gluconate or calcium chlorid. Secondly, the synergism of calcium and digitalis, proved by experiments on animals, may possibly be utilized in the treatment of congestive heart failure. Such treatment was advocated by Billigheimer.[2] He observed that intravenous injection of a 10% solution of calcium chlorid led to bradycardia, which reached its lowest point within 2 or 3 minutes, and which lasted 25 to 30 minutes. When the same calcium injection was given to a digitalized patient, however, bradycardia lasted from 4 to 5 hours. It remains for future investigations to determine whether such combined treatment is of real value in the treatment of the failing heart.

Summary. 1. Intravenous injection of 10 cc. of a 20% calcium gluconate solution produced changes in the electrocardiograms of 26 normal individuals.

2. These changes consisted of flattening or inversion of the *T* waves in 92% of the cases, flattening or inversion of the *P* waves in 54%, and a marked bradycardia in 67%.

3. Intravenous injection of 10 cc. of physiologic salt solution given to 18 normal individuals had no effect whatsoever on the electrocardiograms.

4. This investigation, for the first time, supplies experimental proof of the effect of calcium on the normal human heart.

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BOOK REVIEWS AND NOTICES

THE PRINCIPLES AND PRACTICE OF MEDICINE. Designed for the Use of Practitioners and Students of Medicine. Originally written by the Late SIR WILLIAM OSLER, BT., M.D., F.R.S., formerly Fellow of the Royal College of Physicians, London; Regius Professor of Medicine, Oxford, etc. Twelfth edition; revision by THOMAS MCCRAE, M.D., Fellow of the Royal College of Physicians, London; Professor of Medicine, Jefferson Medical College, Philadelphia, etc. Pp. 1196; 22 illustrations and 16 charts. New York: D. Appleton-Century Company, Inc., 1935. Price, $8.50.

FOR almost a half century this work has been *facile princeps* among text books of medicine, and now its editor who has piloted it through a full third of its career has gone to join his beloved Chief! Will another editor be found to carry the work on, in the up-to-date manner that its originator would have required and yet preserving the inimitable style of its author and not "blown about by every wind of doctrine?" How does this latest edition compare with the first in 1892? Though containing 117 more pages, a better, thinner leaf makes this book actually thinner than the first edition, while a smaller margin gives two more lines to the page. The initial quotations from Hippocrates and Plato remain as old friends. As ever, the book starts with Typhoid Fever: the definition and history have the familiar ring of student days; but with Etiology the changes necessarily begin and the Discussion of H and O Antigens and "rough" and "smooth" carry one far from such older statements as "It is difficult to differentiate the typhoid bacillus from the Bacterium coli." In the specific infectious diseases (only 6 of which were of doubtful nature) the 35 are now increased to 63, of which 25 are "of doubtful or unknown etiology." The 12 "Constitutional Diseases" are now distributed—some merely out of the frying pan into the fire—between Diseases of Metabolism and Deficiency Diseases, which were not recognized in 1892, and a few to Infection and Diseases of the Blood. The arrangement of the System Diseases (digestive, respiratory, circulatory, kidneys and nervous system) remains practically unchanged, though the content is far different and progress often is shown by simplification. The nervous system still occupies almost a fifth of the total space. Perhaps the biggest change is in the old Section 7, where 5 diseases of the blood and 4 of the thyroid gland occupied a modest 33 pages. In this last edition, 16 diseases of the blood-forming organs and 6 of the spleen (which before was not given any independent position) now occupy 42 pages, while the glands of internal secretion require another 32 for the most summary handling. In the present edition much has been changed from the 11th; 24 new subjects have been added, 18 "entirely rewritten" and 16 or more new important forms of treatment outlined. And all this without increase in size!

We recommend to our readers an occasional comparison, as indicated above, because it not only is a pleasant excursion into *tempus actum* but also points out the progress that has been made in almost all lines of medicine. In many of these, not punctuated by dramatic episodes such as the discovery of insulin or the liver treatment of pernicious anemia, the imperceptible nature of the progress often fails to impress us with the progress that has been made.

We greet this friend on its critical 43d birthday (or 11th, if we regard a new edition as a February 29th birthday) and wish it many happy returns of the day.

E. K.

MEDICAL TACTICS AND LOGISTICS. By COLONEL GUSTAVUS M. BLECH, Medical Reserve Corps, United States Army, and COLONEL CHARLES LYNCH, Medical Corps, United States Army, Retired. Pp. 205. Springfield, Ill., Charles C Thomas, 1934. Price, $4.00.

WE have here, as indicated by the title, a treatise regarding the movement and the supply of the troops of the Medical Department preliminary to battle, and the activities of those troops during the engagement. The book contains four main sections: (1) Principles of war, with emphasis on tactics, and the organization and functions of the Medical Service at the front; (2) a description of the medical service of an infantry regiment, and of the medical service of an infantry battalion—at halt, on the march, in offensive combat, and in defensive combat; (3) special situations and special organizations, such as medical service with cavalry troops, and the Red Cross—combined with a review of medical tactics; (4) an appendix, covering (*a*) combat orders illustrated by actual field orders and administrative orders, (*b*) facsimiles of various field medical records, (*c*) reference tables giving marching distances, effective range of weapons, and (*d*) a glossary of military terms.

The book is an excellent one. The first, third and fourth sections contain information generally similar to that given in Army Medical Bulletin No. 14 and certain later Bulletins, and in the recently published semiofficial *Military Medical Manual*, but they are written with a vigorous style, and with a certain amount of new grouping of subject matter, together with inclusion of general military principles, that makes the book very instructive and interesting. The second section deserves special mention because it comprises a series of descriptions, in narrative form, of the service of the Medical Detachment of an infantry regiment, in times of bivouac, offensive combat and defensive combat. These incidents are excellently done, with a good critique in each instance. The characters of Major Sharp (the keen regimental surgeon), of Captain Cleaner, the battalion surgeon interested in sanitation, of Captain Crown, the dental officer, and of Lieutenant Sound, who is appropriately expert with a sound, are illustrated by their daily actions as the reader is carried through several days of battle, in which actual combat oders governing the troop movements give precise information.

A comparison of this book with pre-World War treatises, such as those of Munson, and Straub, gives a striking exposition of the advance in knowledge of the military art, especially regarding the medical service of troops in the field, which has taken place. The authors have learned their lesson in definite part by practical experience, and they show a real desire to transmit their knowledge to their fellow medical officers.

W. C.

LACTOBACILLUS ACIDOPHILUS AND ITS THERAPEUTIC APPLICATION. By LEO RETTGER, PH.D., LL.D., Professor of Bacteriology in Yale University, MAURICE N. LEVY, M.D., Practicing Physician, Bridgeport, Conn., LOUIS WEINSTEIN, PH.D., and JAMES E. WEISS, PH.D., Research Fellows in Yale University. Pp. 203. New Haven: Yale University Press, 1935. Price, $2.50.

THE authors, in addition to presenting details of their bacteriologic methods, outline their experiences with Lactobacillus acidophilus therapy in various intestinal conditions. They report that 31 of 40 cases of simple constipation and 13 of 17 patients with constipation complicated by biliary symptoms were definitely benefited. Success roughly paralleled ability to have acidophilus organisms persist in large amounts in the patient's bowel. The authors were also able to relieve 6 of 8 cases of "mucous colitis" and 7 of 8 cases of ulcerative colitis. In these, however, full benefit was obtained

only so long as treatment was continued. Many of the patients treated for constipation were reëxamined 11 to 18 months after discontinuing treatment. The majority of these had persisting relief and their stools contained the bacilli in high concentration. It is unfortunate that the patients with ulcerative colitis were not studied in more detail immediately before treatment was begun and after relief of symptoms was obtained. The authors seemed quite aware of the lack of diagnostic criteria in many of their cases with supposed biliary disease. The inclusion of such controversial items as the discussions of the etiology of constipation and of "mucous colitis" seems unnecessary in a work of this purpose. These defects do not detract from the value of this presentation of accurate studies of the results of acidophilus therapy in constipation. One may criticize the therapy itself, however, on the grounds that it apparently does not treat the cause of constipation and that, even in the hands of a competent group, does not seem to give relief in a higher percentage of cases than do other forms of treatment. H. T.

PUERPERAL GYNECOLOGY. By J. L. BUBIS, M.D., F.A.C.S., Consultant in Obstetrics and Gynecologist, Mt. Sinai Hospital, Cleveland; Member of Central Association of Obstetricians and Gynecologists. Foreword by P. BROOKE BLAND, M.D., Professor of Obstetrics, Jefferson Medical College, Philadelphia. Pp. 199; 81 illustrations and 2 tables. Baltimore: William Wood & Co., 1935. Price, $3.50.

THIS book is written to advocate the repair of old and recent childbirth injuries either immediately, or within a few days, after delivery. Statistics are presented to show that in the hands of the author and his staff the morbidity and mortality rates are exceedingly low and the final results eminently satisfactory. While immediate repair is the rule, several indications are listed for postponement from 1 to 7 days. In a series of 1326 full-term deliveries, 82.7% were operated upon immediately after parturition and 15.6% within 7 days. The author's account of the ease and safety with which these radical procedures are executed is dangerous teaching, and will not meet with the approval of most obstetricians. Many of the illustrations are semi-diagrammatic and are well done. Those depicting the pelvic muscular and fascial layers are particularly clear. The description of pelvic anatomy and physiology is simple and comprehensive and the chapter on the conduct of delivery contains many valuable suggestions. For a publication of this type, too much space is devoted to prenatal care and obstetric analgesia and anesthesia. The chapters dealing with the cervix and its repair are well written, although the author would probably see fewer cervical fistulæ is less radical immediate postpartum repairs were done. In the section upon injuries to the urethra and anterior wall, discussion of immediate cystocele repair contains the following statement: "In the hands of a novice, there may be a great loss of time and much bleeding may result." This sentence is characteristic of the manner in which the dangers and difficulties of the proposed procedures are minimized throughout the book. Too little space is devoted to exact technical descriptions of the various plastic operations. Such procedures are fraught with difficulties, yet the reader finds few suggestions for avoiding these pitfalls. The sections upon care following delivery and repair, and upon postnatal office treatment contain many valuable hints, obviously the product of many years of experience. The subject of backache, however, is dismissed with one sentence. The last chapters are devoted to consideration of morbidity and mortality figures and to the economic aspect of puerperal gynecologic operations as advocated by the author. It appears that one of consummate technical skill and unlimited facilities can pursue this plan safely, but in the hands of the average obstetrician its hazards far exceed its advantages. F. P.

THE MEDICAL MAN AND THE WITCH DURING THE RENAISSANCE. The Hideyo Noguchi Lectures. Third Series, vol. 2 of the Publications of the Institute of the History of Medicine, The Johns Hopkins University. By GREGORY ZILBOORG, M.D. Pp. 215; illustrated. Baltimore: The Johns Hopkins Press, 1935. Price, $2.50.

THE three lectures that make up this book explore three phases of the thesis that witchcraft is "the central problem of occidental psychiatry." As Sigerist points out in the Preface, the history of psychiatry is especially difficult to grasp because the mental reactions of the psychopath of former times were not, as is often assumed, the same as those of the writer's time. The first lecture is on the *Malleus Maleficarum*, which as the leading textbook of the Inquisition appeared in 19 editions through three centuries. Though men have believed in demons since time immemorial, it was not until the all-powerful Church came to recognize witches as its enemy that persecution became widespread. The Bull of Innocent VIII, here quoted at length, in 1484 sent the Inquisitors, Kraemer and Springer, to suppress witchcraft in Germany and they wrote the *Malleus* to aid them in their task. Though one may shudder at the cruelty that sent many a poor psychopath to the stake, one should not forget that it was the times and not the authors of this book that were out of joint: the mass of intelligent opinion strongly upheld their conscientious zeal. The Church, the chief supporter of the witchcraft tradition, merely carried on the work, as did our own Puritans in Salem and elsewhere. The second of the three parts of the *Malleus* which details many "clinical histories" also makes interesting reading.

In the second lecture on *Medicine and the Witch in the 16th Century* are set forth the efforts to consider the mentally possessed more rationally, even though such clear observers as John Lange, Paré and Fernel were firm believers in the personal participation of the devil in the manifestations of insanity. To the wild inventions of Paracelsus' *De morbis amentium* and the derision of Rabelais and Montaigne were added the clear observation and reasoning of such physicians as Cornelius Agrippa, Vives of Valencia, Levinus Lemnius and Nicolas Lepois—all tending to demonstrate that all "demonopathies" were the results of physical causes.

The third lecture, that occupies a good half of the book, is on that great humanitarian, Johann Weyer, the founder of Modern Psychiatry. His *De praestagiis daemonum* (1563) combats the demonic nature of mental disease, at first destructively with theologic and philosophic arguments, then constructively with keen psychologic and medical observation. As Weyer himself foresaw, his book was placed on the prohibited list and at the time opposed by most of his medical confrères. However, to some it appealed favorably and in the next century his influence was firmly fixed. We agree with the lecturer that Weyer's greatest significance lies in the fact that "he was the first medical man to insist that normal and pathological mental processes differ in degree and form but not in substance." E. K.

DIE WERKE DES HIPPOKRATES. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STRICKER, Würzburg. Book 6 (Pp. 84; illustrated; price, Rm. 7.50), Luft, Wasser und Ortslage (Air, Waters and Places); Book 9 (Pp. 95; price, Rm. 7), Die Diät (Lebensordnung) in akuten Krankheiten (Diet in Acute Diseases). Stuttgart: Hippokrates-Verlag, G.M.B.H., 1934. (To be published in 25 parts costing ca. Rm. 100, card binding.)

REGARDED universally (except by Haller) as one of the "real" (*i. e.*, generally accepted as written by Hippocrates himself) works of Hippocrates

and also our oldest study of the relationship of man to his environment. Book 6 on Air, Waters and Places is of peculiar interest today when this point of view is again receiving close study by medical scientists. The tremendously important questions of the effect of seasons and climates of various places, both in producing different races of men, and in promoting various diseases, is still far from solution; and while, as usual, one will find much that is fantastic in the light of modern knowledge, one will also find much sage common sense in this work. *Inter alia*, it is recognized that no disease is more divine than another: "all are the effect of natural causes." The Editor of this edition makes a strong case for the view that this work with those on Diet and on Winds brings to us a collective presentation from the Hippocratic School of general etiology and therapy. The German translation, based on the text of the *Corpus Medicorum Graecorum* (1927), has the philologic support of Franz Lommer and Prof. Rehm of Munich. One of the appendices gives an interesting discussion of an early manuscript on "Winds" (London Papyrus 137, Ebers), discovered in 1891.

Another of the "real" Hippocratic works, Book 9 on Diet in Acute Diseases, gives in masterly style the régime (*i. e.*, not the complete therapy) to be followed in restoring to health the subject of an acute disease. An error at the beginning does less harm than at the climax; the diet should be rigorous; ptisanes, either non-filtered or their essence (filtered and more easily digestible) should not be given in crises; the proper use of wine, hydromel, oxymel, water and baths is explained; as according to the law of habit all change is harmful, the resumption of food after the crisis must be done very carefully; the art of medicine should not be explored with theories, such as the four humors, but by the observation of how the actual patient reacts to disease. The book starts with an attack on the Cnidian methods of minute descriptions of symptoms without interpretations or applications—one of the few polemics in the Hippocratic corpus. In passing, one cannot but conjecture whether we Americans are not the Cnidians of our time, in our great urge for objectivity and frequent timidity in advancing hypotheses. The present German translation is based on Kühlewein's text (Teubner, 1894), with further reference to the Codices and with the occasional help of Anton Fingerle. E. K.

RÖNTGENBEFUND UND PATHOLOGISCH-ANATOMISCHER BEFUND BEI LUNGENKRANKHEITEN. By DR. MED. MAX VERSÉ, o. ö. Professor der allgemeinen Pathologie und pathologischen Anatomie; Direktor des pathologischen Instituts der Universität Marburg. Versuch einer kritischen Vergleichung. Volume I, text, pp. 93; Volume II, Atlas, 144 illustrations. Berlin: Otto Elsner Verlagsgesellschaft m. b. H., 1935. Price: Rm. 18.

THIS interesting work comprises 2 volumes, brief and easily read. The first volume summarizes 54 cases of pulmonary disease including atelectasis, infarction, pneumonia, tuberculosis, bronchiectasis and lung tumors. For each case there is a short account of the history, Roentgen ray picture during life, Roentgen ray picture of the inflated lungs after death and the autopsy findings. The second volume consists of 144 plates of Roentgen films and postmortem specimens illustrating these cases.

The author attempts to answer the question, "To what extent does the *x*-ray identify structural changes in the lungs?" and its converse, "How do the structural changes in the lungs, as found at autopsy, appear on *x*-ray examination?" The relationship of roentgenographic signs to postmortem pathology is clearly presented, chiefly through the medium of the really excellent illustrations. To the roentgenologist, this book is of undoubted value for reference and to others it is a simple guide to the interpretation of the chest Roentgen ray. L. L.

DIE STÖRUNGEN DES LICHTREFLEXES DER PUPILLE BEI DEN LUETISCHEN ERKRANKUNGEN DES ZENTRALNERVENSYSTEMS. Beiträge zur Frühdiagnostik der Lues nervosa. DR. MED. OTTO LÖWENSTEIN, seither ordentl. Prof. und Direktor des pathopsychologischen Instituts der Universität Bonn, etc. Pp. 92, 31 illustrations. Basel: Benno Schwabe & Co., 1935. Price, Fr. 5.

THE author photographs the direct and consensual reflexes of the pupil on moving picture film and, by projecting the finished picture on a suitable screen, is able to measure the details of the reactions and their time relations. He claims to be able, by this method, to detect disturbances in the pupillary reactions in syphilis much earlier in the disease. The methods employed, even though simplified from his earlier apparatus, are hardly applicable for clinical use, and the classification of various pupillary disturbances is complex. F. A.

THE TREATMENT OF DIABETES MELLITUS. By ELLIOTT P. JOSLIN, M.D. (HARVARD), M.A. (YALE), Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. With the coöperation of HOWARD F. ROOT, M.D., PRISCILLA WHITE, M.D., and ALEXANDER MARBLE, M.D. Pp. 620; 7 illustrations and 144 tables. Fifth edition, revised and rewritten. Philadelphia: Lea & Febiger, 1935. Price, $6.00.

THE medical profession will welcome the new fifth edition of this well-known book. The author's practical experience extending over 37 years and with some 13,000 cases, and his consummate skill in presenting his material in an impressive and interesting way, make this book not only the standard work on diabetes but also one of the outstanding medical texts in the English language. R. K.

NEW BOOKS.

The Autonomic Nervous System. Anatomy, Physiology, and Surgical Treatment. By JAMES C. WHITE, M.D., Assistant Professor and Tutor in Surgery, Harvard Medical School; Assistant Visiting Surgeon, Massachusetts General Hospital, Boston. Pp. 386; 96 illustrations. New York: The Macmillan Company, 1935. Price, $7.00.

The Range of Human Capacities. By DAVID WECHSLER, PH.D., Chief Psychologist, Psychiatric Division, Bellevue Hospital, New York City. Pp. 159; 11 figures and 22 tables. Baltimore: The Williams & Wilkins Company, 1935. Price, $2.50.

Classical Contributions to Obstetrics and Gynecology. By HERBERT THOMS, M.D., F.A.C.S., Associate Professor of Obstetrics and Gynecology, Yale University. With a Foreword by HOWARD A. KELLY, Emeritus Professor of Gynecology, Johns Hopkins University. Pp. 265; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

The Treatment of Acute Poisoning. By H. L. MARRIOTT, M.D., M.R.C.P., LOND., Resident Medical Officer, The Middlesex Hospital, London; Assistant Physician, The Miller General Hospital, Greenwich. Pp. 45; 15 illustrations. London: John Murray for The Middlesex Hospital Press, 1935. Price, 5/–.

John Whitridge Williams. Academic Aspects and Bibliography. By J. MORRIS SLEMONS. Pp. 109; 1 illustration. Baltimore: The Johns Hopkins Press, 1935. Price, $1.50.

Diet and Die. By Carl Malmberg. Pp. 149. New York: Hillman-Curl, Inc., 1935. Price, $1.50.

Russell A. Hibbs. Pioneer in Orthopedic Surgery, 1869–1932. By GEORGE M. GOODWIN. Pp. 136; illustrated. New York: Columbia University Press, 1935. Price, $2.00.

The Obstetric Pelvis. By HERBERT THOMS, M.D., F.A.C.S., Associate Professor of Obstetrics and Gynecology. The School of Medicine, Yale University. Pp. 115; 50 illustrations. Baltimore: The Williams & Wilkins Company, 1935. Price, $2.50.

Man, the Unknown. By ALEXIS CARREL. Pp. 346. New York: Harper & Bros., 1935. Price, $3.50.

Obstetrical Practice. By ALFRED C. BECK, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Pp. 702; 1053 illustrations. Baltimore: The Williams & Wilkins Company, 1935. Price, $7.00.

The Human Foot. Its Evolution, Physiology and Functional Disorders. By DUDLEY C. MORTON, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 244; 100 illustrations. New York: Columbia University Press, 1935. Price, $3.00.

Die Theoretischen Grundlagen und Möglichkeiten der Röntgendiagnostischen Weichteiluntersuchung. Forty-eighth Supplementary Volume of Fortschritte auf dem Gebiete der Röntgenstrahlen. By DR. ADOLF ZUPPINGER Pp. 99; 46 illustrations. Leipzig: Georg Thieme, 1935. Price, Paper, Rm. 16; Bound, Rm. 18.

Prescription Writing and Formulary. The Art of Prescribing. By CHARLES SOLOMON, M.D., Assistant Clinical Professor of Medicine, Long Island College of Medicine; Associate Attending Physician and Chief of the Medical Clinic, Jewish Hospital of Brooklyn, etc. With a Foreword by LEWELLYS F. BARKER, M.D. Pp. 351; 32 illustrations. Philadelphia: J. B. Lippincott Company, 1935. Price, $4.00.

Libra Jubilar del Profesor Bernardo A. Houssay, 1910–1934. Volume X, Supplement, November, 1934, of Revista de la Sociedad Argentina de Biologia. Pp. 583; illustrated. Buenos Aires: Imprenta Ammorrortu, 1935. (Price not given.)

A Terminology of Operations of the University of Chicago Clinics. By HILGER PERRY JENKINS, M.D. Pp. 99. Chicago: The University of Chicago Press, 1935. Price, $1.00.

A Suggestion for an Experimental Trial of Alum-treated Bactericidally Inactivated Virus in the Active Local Immunization Against Poliomyelitis. By S. PESKIND, B.S., M.D., Pp. 6. Cleveland: The S. P. Mount Printing Company, 1935. (Price not given.)

Celsus de Medicina. In Two Volumes. Volume 1. With an English Translation by W. G. SPENCER, M.S. LOND., F.R.C.S., ENG. Pp. 499. Cambridge: Harvard University Press, 1935. Price, $2.50.

Hugh Owen Thomas. A Personal Study. By FREDERICK WATSON. Pp. 94; illustrated. New York: Oxford University Press, 1934. Price, $4.25.

Behavior Developments in Infants. A Survey of the Literature on Prenatal and Postnatal Activity 1920–1934. By EVELYN DEWEY. Pp. 321. New York: Columbia University Press for the Josiah Macy, Jr., Foundation, 1935. Price, $3.50.

Localized Rarefying Conditions of Bone as exemplified by Legg-Perthes' disease, Osgood-Schlatter's disease, Kümmell's disease and related conditions. By E. S. J. KING, M.D., D.Sc., M.S. (MELB.), F.R.C.S. (ENG.), F.R.A.C.S., Honorary Surgeon to Out-Patients, Melbourne Hospital; Stewart Lecturer in Pathology, University of Melbourne. Pp. 400; 70 illustrations. Baltimore: William Wood & Co., 1935. Price, $7.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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LEUKOPENIC STATES.

THE neglect attending the study of neutropenic states prior to 1922 was suddenly turned into keen interest by the report of Schultz,[1] in that year, of the disease entity now known as agranulocytic angina. True, the diagnostic value of leukopenia in such diseases as measles, malaria, typhoid fever and influenza was universally recognized, but interest in, and investigation of, the mechanism of the response attracted little attention. However, since 1922, the literature upon this subject has grown to tremendous proportions.

Schultz believed the clinical state he described was a new syndrome, characterized by a rapidly fatal course, a marked reduction in the circulating granulocytes, and ulcerative lesions in the mouth, vagina, and rectum. It is well known now that an undoubted case can be traced back to 1902, when Brown described "A Fatal Case of Acute Primary Infectious Pharyngitis with Extreme Leucopenia."[2] Many attempts have been made to trace the disease picture beyond Brown's report. The latest of these, an historical review by Stenn,[3] draws attention to cases with clinical characteristics resembling agranulocytic angina recorded in the time of Hippocrates. The diagnosis of "putrid sore throat," commonly made in the 19th century, included the proper clinical attributes. These cases, Stenn states, possessed the identical clinical picture and "there is no reason to believe that the latter (agranulocytic angina), was ushered into existence with the birth of the 20th century." While the disease may have existed from time immemorial and had to wait for the development of modern hematologic technique for its recognition, the utter impossibility of differentiating it from such conditions as aleukemic leukemia and Vincent's angina, on clinical grounds alone, together with recent observations relating to its etiology, point strongly to the possibility of its having been "ushered into existence with the birth of the 20th century."

Etiology. The 13 years that have elapsed since Schultz' report have led us through an extremely confused state in the recognition and classification of leukopenic states, until at present differential diagnosis rests upon sound criteria. Etiologic considerations and pathologic physiology, however, still rest upon uncertain grounds. Confusion

in the understanding of agranulocytosis is due, in part, to the many terms used. Schultz named the syndrome agranulocytosis. Friedemann[4] preferred agranulocytic angina. For etymologic reasons others have changed the nomenclature, until we now find such terms as granulopenia, granulocytopenia, neutropenia, malignant neutropenia, neutrocytopenia, and pernicious leukopenia in common use.

Roberts and Kracke[5] have put forth a simple classification of granulopenia into complete and incomplete varieties. The incomplete variety is common and not very dangerous, the complete variety rare and dangerous. The mechanism of the complete type is described[6] in 5 stages, which occur "with inevitable and inexorable regularity." First, there is the bone marrow onset, a selective failure of the bone marrow which may be myelocytic aplasia, myeloblastic dysfunction, cessation of maturation, allergy, or some other factor. Second, about 4 days after the bone marrow failure the blood stream onset occurs, followed third, by the clinical onset, fourth by secondary bacterial invasion, and fifth either by return of granulocytes or by death.

While such a dichotomous classification may be most important in arriving at a quick diagnosis as a guide to prognosis and treatment, a further elaboration is necessary to an understanding of the etiologic aspects of granulopenia. A simple classification, as outlined by Sturgis[7] divides granulopenia into primary and secondary types. The primary type is subdivided into: (*a*) the acute (Schultz) type with an abrupt onset and course, and (*b*) a chronic recurrent variety characterized by many attacks. The secondary type differs entirely from the primary variety and is observed most often in arsenic or benzol poisoning, following irradiation, in various infections such as pneumonia, and in certain blood diseases such as pernicious anemia, aleukemic leukemia, and aplastic anemia.

Kastlin[8] and Pepper[9] have pointed out that leukopenia may be produced in three ways: 1, increased white blood cell destruction; 2, failure of production, or 3, migration of cells from the peripheral blood upon which counts are made. The first mechanism may play a part in some cases but the second appears to be a frequent mechanism, for example, in aplastic anemia. The third, Pepper states, is usually transitory but quantitatively it may be very striking. It is the mechanism usually concerned when foreign protein enters the blood. Granulocytes leave the blood to go to the liver and spleen.

A distinct shift in interest in the theories of the etiology of agranulocytosis has occurred in the past 2 years. The association of infectious processes with the syndrome at first led to the supposition that the organisms isolated were the causative agents. Reproduction of the disease with such organisms in pure culture uniformly failed, but changes in the white blood count were produced with bacterial products (foreign proteins) and with organisms placed in parchment capsules implanted in animals.[10] Confirmation of these results has not been uniform.[11] Studies on recurrent cases revealed that the characteristic blood picture developed prior to the onset of infection and clinical symptoms, and have apparently dealt a death blow to the infectious theory. A recent case report by Kitchin[12] confirms this sequence of events. He followed a recurrent case and by plotting the granular cell count and the spirochetal condition of the mouth showed an increase

in Vincent's organisms following the lowered granulocyte count, indicating that the number of neutrophils in the peripheral blood stream is important in the control of the bacterial growth in the gingival crevices. At present infection is regarded, as stated previously in Kracke's theory, as evidence of secondary invasion in an organism stripped of its defense powers (leukocytes). The pendulum in the clock of interest has swung then, from infection to drugs and chemicals as a possible cause.

Fitz-Hugh[13] states that since 1928 Pepper has, upon clinical grounds, suspected the importance of allergy in agranulocytosis. His views are based upon the occurrence of the clinical picture in patients with definite allergic backgrounds. We do know, from the work of Vaughn,[14] that allergens have a distinct effect in lowering the white blood count. He introduced the production of leukopenia (leukopenic index) as a diagnostic procedure in the determination of the allergenic properties of foods following their ingestion by patients. But it remained for Kracke[15] and Madison and Squier[16] definitely to incriminate specific agents as important etiologic factors. Kracke noted the frequency of occurrence following the ingestion of coal tar derivatives. Madison and Squier definitely accused amidopyrin as the cause. At the same time, and independently, Rawls*[17] had noted, in the use of drugs containing the benzene ring in the treatment of arthritis, that 2 patients developed agranulocytosis. He cautioned us in the use of amidopyrin. Since these reports numerous cases have been placed on record [18–25] demonstrating the importance of amidopyrin in the development of agranulocytosis, and previously reported series have been restudied in this light. In Madison and Squier's first report they described 13 cases, all having taken drugs containing benzene ring derivatives over a period of time preceding the onset of symptoms. Five of these patients received such drugs during treatment; 4 (80%) died; 8 avoided such drugs; only 2 (25%) of these died. Two patients showed a drop in their white counts following the ingestion of single doses. Experimentally, of 11 rabbits given the drugs only 1 developed an agranulocytic blood picture. It died on the thirtieth day.

Plum[19] in reviewing the literature found, from May, 1933 to December 1934, 128 cases reported due to amidopyrin. This number has increased remarkably since then. He, as well as others,[20,21] has repeated the experiment of Madison and Squier, in giving patients amidopyrin subsequent to recovery. In Plum's case detailed blood counts are available. In 1½ hours the white blood count dropped from 9000 to 1900, to rise in 3 hours to 11,500 and again drop to 2000 within the first 24 hours. Gradually, in the next 10 days the count rose to 10,000. The transitory rise, not described by the other observers, was accompanied by a distinct "shift to the left." Plum also found a temporary fall in the non-granular series, followed by a rise within 24 hours and a return to a maximum in 10 days.

A most ardent adherent to the benzene ring theory has been R. Kracke. In a recent report[22] he reiterates his stand and gives evidence to support his previous work. He points out that only in those barbiturates containing the benzene ring have cases of agranulocytosis

* In a more recent communication, now in press, Rawls stresses the infrequency of amidopyrin cases in a large series of agranulocytoses.—EDITOR.

appeared. He likewise insists that occasionally in the use of neoarsphenamin a case develops without depression of other hematopoietic elements. In French reports following the use of gold salts agranulocytosis occurred only in those patients receiving a gold salt containing a benzene ring. The presence of an amine, NH_2, group he believes, merely facilitates the oxidation process. All these drugs, theoretically, may be oxidized to quinone and catechol. To substantiate this contention the oxidation products have been injected into 17 rabbits. Of 6 surviving the injections, 1 showed marked leukocytic depression and 2 showed complete agranulocytosis. Recently, dinitrophenol has been added to the list.[26-29]

To further the chain of circumstantial evidence convicting amidopyrin and allied drugs, Kracke points out that most of these drugs were introduced about 1922. Furthermore, the disease is most prevalent in the United States and Germany, countries where these drugs, anilin dyes, and coal tar compounds are most commonly used. The disease is also most common in those groups to whom these drugs are most accessible, such as physicians, nurses, druggists, dentists and housewives.

Herz,[30] like Kracke, believes that amidopyrin is an important cause of agranulocytosis, but does not believe that the benzene ring is responsible. To him the NH (imido) component is the toxic element regardless of whether it remains as NH or whether H is replaced by another radical. The NO_2 radical of dinitrophenol he considers just as toxic as NH_2. Since dinitrophenol, arsphenamin and amidopyrin all contain both groups it is difficult to say, *a priori*, which group produces the toxicity.

In spite of all the enthusiasm and evidence pointing to the amidopyrin group as the cause of this syndrome there is good evidence to show that some cases are entirely unrelated to the use of drugs. Jackson[31] admonishes that in the consideration of etiologic agents in any condition, chance alone may play havoc with reasoning. Amidopyrin is a commonly used drug. Custer[32] informs us that in the Philadelphia General Hospital in 29,488 admissions (4027 deaths), 120,000 tablets of amidopyrin were used. There were no instances of agranulocytic angina in the wards nor in the 1926 autopsies performed in this period. Cases definitely known to have taken no such drugs are on record.[31,33] In Jackson's group, there were 27 cases with accurate evidence of the use of amidopyrin. Seven of these received the drug before the onset of symptoms, which could possibly have developed from its use. Twelve patients (44%) received no drugs before, during, or after the onset of agranulocytosis. Yet they had clinical pictures similar to those who took the drug. Cases have been reported with the neutropenia corresponding to the first of each menstrual period,[34] in kala-azar,[36,37] acute pemphigus,[35] and following influenza.[5]

Fitz-Hugh[13] feels that "drug idiosyncrasy and the orthodox dictum of agranulocytosis preceding the onset of symptoms clashes hopelessly in the face of certain acute and relapsing cases reported." He furthermore points out that a neutropenic effect from amidopyrin cannot be a simple toxicologic problem for less than one in thousands of users of amidopyrin develop the disease; those who develop the disease do not take the drug in excess; and patients who have taken the drug in excess (allonal suicides, patients with measles and rheumatic fever)

maintained normal blood counts. However, an allergic or susceptible individual may be necessary, in whom only small doses suffice. This is the view of Madison and Squier.[38] They believe that the blood changes in agranulocytosis result from repeated administration of these drugs, especially amidopyrin, to persons who have developed specific allergic drug hypersensitivity through use of these products. Skin sensitivity was demonstrated by patch tests in 2 cases, and systemic reactions resulted in these patients, with reduction of the total and granular counts and elevation of the temperature, following application of a 10% solution to the unabraded skin. They considered the risk of intracutaneous tests too great to attempt their use.

One must confess that amidopyrin often appears to be at least the exciting cause of the disease, and in several cases the use of the drug after recovery has shown distinct effects upon the white blood count. One cannot deny that amidopyrin often appears to cause the clinical picture, but an identical clinical picture may develop without its use.

The possibility of an endocrine factor must be considered in view of several recent case reports.[34,39] Chronic recurrent agranulocytosis has been shown at times to have a definite temporal relationship to the menstrual cycle. While the relationship is not constant, Jackson and Merrill have been impressed by cases with attacks at, or about, the menstrual cycle. Furthermore, approximately 80% of cases occur in women. Thompson has followed 40 cases for a possible temporal correlation of the onset of the granulocytopenia with the onset of menstruation: 25 were under 40 years of age, that is, in the menstrual age; 17 of these patients dated the onset of subjective symptoms within 1 or 2 days of the regular menstrual period, and all 17 were menstruating on admission to the hospital. In 6 there were one or more recurrences coincident with the menses.

One cyclic case, a man, reported by Thompson, developed diabetes insipidus. Hormonal studies suggested that the granulocytopenia occurred in this man at the time of the hormonal catamenia.

The experiments of Orr[40] suggest that the thyroid plays little or no rôle in endocrine-conditioned cases. He has shown in thyroidectomized rabbits that the myeloid tissue is less and the lymphoid tissue more vulnerable to the toxic action of benzene that in the normal, and that the response of the neutrophils and myeloid tissue to stimuli provoking leukocytosis, such as infection and nucleic acid administration, is unaffected by thyroidectomy.

The recent work of Miller and Rhoads[41] attacks the problems of etiology from an entirely different aspect. In a study of black-tongue, they found that animals dying of the disease in an acute form frequently showed leukopenia with the acute stomatitis. In certain instances they describe the appearance or oral lesions strikingly similar to those seen in agranulocytic angina in humans. However, the leukopenia developed together with, or soon after, the onset of the mouth lesions, and no evidence is offered to show that the stomatitis followed the leukopenia. Furthermore, in none of the animals was complete agranulocytosis present. The lowest total white count was 1250, and the lowest absolute neutrophil count 360. Pathologically, bone marrow alterations were found, including a defect in the maturation of the erythropoietic cells. However, duration of the change was apparently too short to be reflected in the blood stream.

In spite of the close relationship of some cases of agranulocytosis to the intake of amidopyrin and related chemicals, it must be said that the etiology is still unknown. Certain cases follow specific diseases (kala-azar, influenza) and others appear to occur without apparent cause. Can all these seemingly unrelated cases be reconciled to one common etiologic factor? Is agranulocytosis a specific disease or a syndrome? As yet the question is unanswerable.

Pathology. The pathology of agranulocytic angina is as confused as the etiology and treatment. This disordered state can be explained in part by two facts. First, those cases diagnosed as agranulocytosis have not, as scrutiny and reflection on the reported cases will show, always met the rigid criteria we now maintain in diagnosis. Second, and most importantly, the selection of material for study has not been carried out with care.

Custer[32] stresses the importance of meticulous care in the examination of the bone marrow. Obviously, definite criteria must be laid down in obtaining specimens to ensure adequate data for analysis. Marrow from more than one focus must be included in the examination, preferably a specimen of the normally fatty type (femur, tibia) and one from the more cellular areas (ribs, vertebræ, sternum). Sections are essential. Smears alone, Custer states, are nearly valueless for the relative proportion of cells and their relationship to each other are disturbed and cannot be estimated.

With the above facts in mind recent investigations have begun to change the concept of the pathology, and, consequently, the fundamental nature of agranulocytosis. The former contention that aplasia of the marrow is the characteristic lesion is gradually giving way, under this rigid technique, to the view that the difficulty lies in "maturation arrest." This view was first proposed by Fitz-Hugh and Krumbhaar[42] who described a maturation arrest at the stem-cell stage followed by a terminal stage of aplasia. Jaffé[43] at a later date reported findings of increased cellularity in the bone marrow with a predominance of myelocytes of changed staining characteristics. Others have noted similar findings.[44,45] Jackson and Parker[46] agree in general with these views. In 25 cases, they found the cellularity was usually normal. In later stages of the disease in some cases degrees of hypoplasia were found. Little or no disturbance occurred and no abnormal features were noted in the red cell series. Megakaryocytes were normal in number and histology. No mature granulocytes were found in any marrow and there were no myelocytes. They, as did Fitz-Hugh and Krumbhaar, found active mitoses in the stem cells, indicating maturation arrest. However, in those patients surviving 8 to 20 days, the picture of relative hypoplasia developed.

More recently, Custer[32] has analyzed 11 cases under rigid clinical and pathologic scrutiny. His findings are similar to those of Fitz-Hugh and Krumbhaar, and Jackson. In 9 of the 11 cases the following pathologic findings occurred uniformly—1, marked proliferation of myeloblasts; 2, failure of these cells to mature; 3, normal or slightly increased red blood cell formation; 4, slight hyperplasia of otherwise normal megakaryocytes; and 5, infiltration of lymphocytes and plasmocytes. In the 2 remaining cases degeneration and relative hypoplasia were noted although changes, qualitatively, were similar to the other 9.

As in the reports of Fitz-Hugh and Krumbhaar, myeloblasts represented almost entirely the granulocytic series. While the degree of cellularity varied considerably in different bones in individual cases, the qualitative changes were similar. He states that "the paramount feature is a failure of actively proliferating myeloblasts to ripen into segmented forms of the neutrophil. Is this due to a lack of an intrinsic maturation factor, as suggested by Fitz-Hugh and Krumbhaar, and comparable to that of the erythron in pernicious anemia, or is it due to extrinsic chemical or bacterial toxin?"

From the standpoint of pathologic bone marrow, Custer has classified the causes of neutropenia, linking the alterations in the blood with changes in the marrow, so that the clinician is offered an opportunity to classify his cases as idiopathic or symptomatic agranulocytosis. The pathologic classification of neutropenias which may be correlated with the classifications given under "Etiology" follows:

"I. With relatively 'full' marrow, as a result of:
- "*a.* Severe toxemia (usually bacterial)
- "*b.* The leukoses (leukemias)
 - "1. Aleukemic myelosis—overproduction of granulocytes
 - "2. Lymphodenosis—replacement of granulopoietic tissue
 - "3. Reticulosis—replacement of granulopoietic tissue
- "*c.* Idiopathic agranulocytosis (Schultz)—defective maturation of the myeloblasts.

"II. With relatively 'empty' marrow as a result of:
- "*a.* Severe toxemia (usually chemical, as benzol)
- "*b.* Marrow exhaustion, through protracted anemia, infection
- "*c.* Aplastic anemia (idiopathic)
- "*d.* Irradiation
- "*e.* Idiopathic agranulocytosis (occasional case)."

These confirmations of the state of the bone marrow make it possible to elaborate upon Kracke's theory of the sequence of events in granulocytopenia, and to assign maturation arrest as the cause of the selective bone-marrow failure. Fitz-Hugh[47] has outlined his concept of the pathologic physiology. Through the toxin, allergy, or whatever influence that suppresses maturation, there first occurs in the leukopoietic centers of the bone marrow an arrest in the development of the parent white blood cell. Maturation and emigration then slow down or cease entirely, and granulocytopenia follows. The granulocytes of the bone marrow are represented then only by myeloblasts with an occasional myelocyte in normal or increased numbers (hyperplastic stage). If these cells later die, the marrow reaches the aplastic stage. Remission, if it occurs, appears to be initiated by release of the maturational arrest, or by some factor which allows leukopoiesis and emigration to be carried out. Granulocytes again appear in the blood stream.

Because of the analogies of this concept to the pathologic physiology of pernicious anemia, Fitz-Hugh and his co-workers have suggested the name pernicious leukopenia for this disease.

Symptomatology. Under this heading I shall consider only a few scattered findings which have come to light in the past 2 years. The majority of these are best considered and naturally fall, in discussion,

in the consideration of diagnosis. When leukopenia is a concomitant of a recognized disease, for example malaria or infectious mononucleosis, the symptoms are those of the disease.

Reflection, on the possible results that may follow the conditions defined in Kracke's theory of the mechanism of agranulocytosis leads one to a basic, symptomologic outline of this disease. Primary onset of the disease in the bone marrow is accompanied at first by no symptoms whatsoever. With the reduction in granulocytes about 4 days later one might expect symptoms arising through the absence of granulocytes. Should we know more fully the functions of the granulocytes, we could expect symptoms due to the suspension of this function.

Without granulocytes, infection is inevitable, for the granular cells represent a most important immunity conferring mechanism. Without them bacterial invasion of the mucous membranes with ulcers, inflammation, fever, and chills is a constant finding. Kracke[5] believes also that the granulocytes are necessary to the individual for his daily normal strength. Without them fatigue, exhaustion, prostration, and even collapse may result. Such symptoms, he finds, are common in individuals with leukopenia. He suggests a definite, but vague, clinical syndrome, consisting chiefly of weakness, easy exhaustion, fatigue and loss of strength associated with a chronic diminution in the number of granulocytes. The same author believes that dulling of mental functions, and loss of memory, leading to delirium and unconsciousness, may be ascribed to absence of granulocytes as well. The fever occurring in agranulocytosis before sepsis suggests to him a rôle of temperature control.

Diagnosis. Diagnosis consists, briefly, of cataloging any particular case with respect to one of the several classifications previously given. This procedure is not and has never been a simple matter. However, in the past 13 years great strides have been made in this direction. Says Kracke, "A leukopenia with complete or near complete absence of granulocytes, which constitutes the essence of the disease granulopenia or agranulocytosis, is one thing, and a leukopenia that is a blood sign of a disease, of which it is a part, is quite another thing. Fine judgment and acumen may be necessary to make the differentiation. Sometimes only waiting will solve the problem. The point to be emphasized is that a low granulocyte count is not, of itself, proof of the disease granulopenia."

Doan emphasized[48,49] the differentiation of the leukopenias in an analysis of his own series. Over 80% of the patients referred to him in a 3-year period had leukopenias not of the Schultz type. Most cases will, no doubt, from analysis of the patients' symptoms and signs, be classified as hematologic accompaniments of specific diseases, such as overwhelming infection (pneumonia, septicemia), infectious mononucleosis, malaria, virus diseases (measles, influenza), irradiation, benzol poisoning, the splenomegalies with leukopenia, aplastic anemias, and others.

One must, of course, have forever in mind the possibility of primary agranulocytosis. It is only through alertness and religious use of the routine laboratory hematologic studies that one can be aware of the possibility of its presence.

Jackson emphasizes that the best hematologic criteria for diagnosis

of granulocytopenia are a greatly reduced white blood count with complete absence of the neutrophils, together with an essentially unimpaired red blood cell and platelet count. Bleeding and palpable spleen and lymph nodes are absent. With local sepsis, however, lymph node enlargement may occur. Kracke,[5] on the other hand, reports a high percentage of patients with hemorrhage. These, he states, are usually small and at times are found at autopsy only. The platelets in these cases have shown marked decreases. The hemorrhagic tendency, as described by Kracke, is secondary to the septic process resulting from the neutropenia. Most authors believe hemorrhage is rare. Throat ulcerations are not characteristic, and may be absent. There should be no other disease present which could logically explain the leukopenia. Confusing cases often arise in aleukemic leukemia. Miliary tuberculosis of the bones[50] has produced a most confusing picture. Hodgkin's disease, metastatic carcinoma and overwhelming sepsis may also follow in general the hematologic criteria given above. Extreme leukopenia alone with absence of granulocytes is not, as Custer's classification points out, pathognomonic of a single pathologic entity.

The 3 cases reported by Jackson, in a discussion of diagnosis,[72] may be read and analyzed profitably by every one interested in the disease. The following statements embody one of Jackson's reports. In leukemia, regardless of the total white count, the blood shows a number of very young cells, usually "blasts." Only occasionally is such a cell found in the blood in agranulocytosis. In agranulocytosis prostration is more marked and the febrile reaction less labile. Final differentiation from aleukemic leukemia rests upon the character of the white cells, changes in the red blood cells and platelets, and bone marrow changes. There are those who feel there is a close connection between the two diseases.[51] Strumia points out that in the two diseases there are many similarities in the clinical course, blood picture and the anatomic lesions. He cites at least 6 reported cases of apparent transition of one disease into the other. If the relationship is true, and what the relationship is, has not as yet been ascertained.

Treatment. Treatment of leukopenic states is rationally that of the etiology. When the etiology is unknown and the cause cannot be removed, treatment usually progresses along two lines: 1, support and symptomatic relief, and 2, empirical measures based chiefly upon theory and analogy to similar diseases. Evaluation of treatment must depend upon the accuracy of diagnosis and here, in granulocytopenia, lies a major problem. Treatment of amidopyrin granulocytopenia while continuing the use of the drug, or injecting pentose nucleotide into a misdiagnosed aleukemic leukemia must, of course, raise havoc with the conclusions as to the efficacy of the procedure carried out. It is with such thoughts in mind that the therapy of primary granulocytopenia must be approached.

Roberts and Kracke[5] outline "three chief objectives of scientific treatment." The first objective concerns itself entirely with the problems of support and symptomatic relief, for the maintenance of life and strength. Nursing care, food, water, control of fever and care of the necrotic lesions are included. Second, attempts to restore the function of the bone marrow and consequently the white blood count to normal must be sought. If maturation arrest is the pathologic state,

a substance comparable to liver or hog stomach in the treatment of pernicious anemia would be the goal. Such a specific is not available. The third objective is warmly disputed. Roberts and Kracke state that sepsis and necrosis are the hopes of every patient to stimulate the myeloblastic activity of the marrow. Jackson and Parker[46] disagree. The disease may develop in the face of existing abscesses. "That sepsis raises the white count in individuals possessing a normal marrow is no indication that it will do the same in one whose bone marrow contains, so far as white cells are concerned, only stem cells. Just how sepsis causes leukocytosis and an hyperplastic marrow in normal patients is not clear. There is no evidence, however, that it does so by stimulating the few existing stem cells to maturation."

The following are the most important procedures currently discussed in the literature in the treatment of agranulocytosis: non-specific measures, pentnucleotide, stimulating doses of Roentgen ray, liver extract, sepsis and necrosis, transfusion, adenin sulphate, leukocytic cream and addisin.

Non-specific measures deal chiefly with the procedures commonly used in producing leukocytosis. Intramuscular turpentine, milk injections, subcutaneous benzene and even bacterial injections have been suggested. Sepsis and necrosis are similar factors concerning which nothing more than the previous discussion need be added. The overwhelming consensus of opinion today is against the use of these measures especially since the establishment of maturation arrest as the pathology of the marrow, for no mature leukocytes are available to be called out.

Pentnucleotide. Henry Jackson[52] first isolated from normal human blood a substance which he believed to be adenin nucleotide combined or mixed with an equal quantity of a pyrimidin nucleotide. Four years later, from the same laboratory came the report[53] that the bone marrow of rabbits was stimulated by these substances to the production of neutrophilic leukocytes. This work started from the hypothesis that the effective normal stimulus to granulocyte production in the peripheral blood was the liberated products from disintegrating cells, possibly nucleic acid derivatives. Reznikoff[54] reached similar conclusions and in 1930[55] treated 4 patients, 3 of whom recovered, with adenin and guanin. In 1931, Jackson *et al.*[56] presented the results of treatment of 20 patients with marked leukopenia with pentose nucleotide; 13 of these patients were diagnosed primary agranulocytosis; in 14 of the 20 patients recovery took place; 7 of the 13 patients with primary agranulocytosis recovered.

Since the pioneer work of Jackson and his coworkers, pentnucleotide has been used extensively throughout the world. Reports of its use, as with other forms of therapy, have been conflicting. Many single case reports and reports of several groups of cases have appeared in the past 2 years, some with, others without, beneficial results. Only by accumulation of cases in numbers sufficient to analyze statistically will it be possible to evaluate this or any other form of therapy. Of 103 patients treated by pentnucleotide mentioned in Jackson's report,[46] 69 (67%) recovered and were still alive. A mortality of 33% is much lower than the mortality in the untreated disease, which is generally conceded to be above 75%.

Experimental data does not bear out clinical results with the use of nucleotide. Kimm and Spies[57] produced experimental leukopenia by irradiation. Pentnucleotide had no apparent effect in the subsequent course of these animals. Reich and Reich[58] in similar experiments produced leukopenia by benzol poisoning in rats. Control experiments were run with saline injections in addition to the pentnucleotide therapy. Results did not differ significantly. While such experiments may cast some doubt on the value of pentnucleotide in the treatment of agranulocytosis, it must be remembered that irradiation and benzol poisoning do not produce the clinical and pathologic entity of primary agranulocytosis. It appears, clinically, that results are better with pentnucleotide than with any other form of therapy. Surely, except for the possibility of some reactions which have occurred, there are no detrimental effects, and every case should be given the benefit of a trial with such therapy.

The action of adenin sulphate, a purine base and a disintegration product of the nucleotides, is thought to be similar to that of the nucleotides. It might be expected that therapeutic results would be similar. Adenin sulphate has not had as extensive use as the pentnucleotides so that a large group of cases is not available for analysis. Reznikoff[59] reported 35 cases which had been followed, 15 of which were definitely diagnosed as "primary" agranulocytosis. Eleven (73%) of the 15 recovered, figures which compare favorably with the results with pentnucleotide. Although adenin sulphate is a simpler chemical compound than pentnucleotide and appears to give a quicker response when effective (24 to 48 hours as compared to 4 to 5 days) it is less soluble, must be boiled in saline, and is given intravenously when warm.

Bone marrow itself has been used in therapy. Reports are scanty[60,61] and no conclusions may be drawn from its casual use. Strumia[62] advocates the use of a leukocytic cream and gives directions for its preparation. Injections were given intramuscularly into 10 patients with agranulocytosis. All the cases recovered. In most cases an increase in circulating granulocytes occurred in 1 to 4 days, usually within 48 hours.

Liver extract, first used with apparent success by Foran, Sheaff and Trimmer[63] has been investigated further by Meyer, Middleton and Thewlis,[64] who believe it probably acts by stimulation of the bone marrow, since the leukocyte count is raised by its use following splenectomy. Martin[65] claims success with liver. Jackson's cases,[46] 4 in number, all died, but these patients received pentnucleotide as well. Heck's case[61] of recurrent agranulocytosis received liver therapy with a response which differed in no way from that occurring in attacks without any treatment at all. Other reports, similar to those given, show approximately the same results. In the evaluation of therapy as yet liver must be given a minor place. As its use continues and a series of cases develops, sufficient material for statistical analysis will settle its value. Today its value cannot be satisfactorily estimated.

Addisin, an hemopoietic substance secreted in the normal stomach, akin if not identical with the intrinsic factor of Castle, and, therefore, related to liver extract, was used in 1 patient by Morris.[66] The white

blood count began to rise in less than 24 hours following the administration of the drug. Further experience with this substance is indicated.

Transfusion. Taussig and Schnoebelen[67] collected 53 cases in which transfusion had been used. Thirty-four (64%) died, as compared with 75% with no specified form of therapy. As a curative measure transfusion appears to offer little help. Its use, however, may be important as a temporary measure in that it may prolong life, and second, by prolonging life it may carry a patient over a period of several days until other therapeutic measures can be instituted, or until spontaneous remission develops.

Irradiation. One reads much of stimulating doses of Roentgen radiation in the treatment of agranulocytosis. The term "stimulating" must be defined. Most radiologists[68] believe that if effective at all Roentgen ray is entirely destructive in its action. Radiation may destroy cells and set free enzymes or disintegrating cellular products, which may secondarily act as stimulating factors. If Roentgen radiation is active in the treatment of agranulocytosis it is, no doubt, by this mechanism, and perhaps even through the production of substances akin to adenin and the nucleotides.

Reports of results with irradiation are conflicting. Doan[48,49] considers that Roentgen ray therapy is always contraindicated in every leukopenic state unless it can be proved that myeloid hyperplasia exists in the marrow. It is contraindicated, then, whenever a hypoplastic myeloid marrow underlies the leukopenic state. Fitz-Hugh[47] gives Roentgen ray if practicable. He states it is certainly harmless and may be of value although experience is not convincing. Reported results are variable. In 64 cases collected by Taussig and Schnoebelen[67] 34 (53%) died. In 4 of their own cases 2 recovered and 2 died. Coggeshall[69] reports a successful case. Gager and Speer[70] treated 2 cases with recovery. Four of 5 of Waters and Firor's cases[71] survived. Jackson is not impressed with the efficacy of radiation.[72]

In general, the statement holds that, although irradiation seems effective in some cases, it has not as yet established itself as an effective form of therapy, and in cases with an aplastic marrow its effects may even be detrimental.

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PEDIATRICS

UNDER THE CHARGE OF
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THE BLOOD PICTURE AND ITS VARIATIONS IN INFANCY AND CHILDHOOD.

A REVIEW of the development of the hematopoietic mechanism is essential to an understanding of the normal blood picture and the abnormal variations which are encountered so often in infants and children. The following is a widely, though not universally, accepted concept. In the embryo, formation of red blood corpuscles precedes the formation of the other cellular elements of the blood. The forerunner of the erythrocyte is the megaloblast. This arises from the endothelial cell, and is present for a considerable time before the leukocytes are differentiated. Prenatally the liver and the spleen are active seats of blood formation, but by the time the child is born the bone marrow has entered into the function of blood production. However, during early infancy these two organs still retain partially their embryonic hematopoietic function. Whenever a demand arises these centers function again to meet the demand. As the child becomes older the function becomes established more definitely in the bone marrow and a demand for additional cellular elements is met largely by it. Embryonic or very immature cells appear less frequently in the circulation. The red cells are produced in bone marrow from the endothelial cells lining the closed vascular sinusoids (Doan). They begin as megaloblasts and become in sequence macroblasts (erythroblasts), normoblasts, reticulocytes and finally the mature erythrocyte. Reproduction by cell division may occur as long as the nucleus remains normal, *i. e.*, the pyknotic nucleus of the normoblast does not allow reproductive cell division. The granular leukocytes originate in bone marrow parenchyma. The lymphocytes are derived from lymphoid tissue and the monocytes (endothelial leukocytes) from the reticuloendothelial tissues.

The blood elements show a marked instability during the first 2 months of life. Merritt and Davidson[1] studied 77 normal children from their birth to 1 year of age. They found that after the second month the erythrocyte count of 4,690,000 persisted throughout the first year with a mean deviation of 370,000. In the same way the mean value for hemoglobin during the first year was found to be 12.6 gm. per 100 cc., with a standard deviation of 1.36 gm. In the Sahli scale, 17 gm. per 100 cc. is equivalent to 100%, and the color index is 0.90. They found also that the reticulocytes in the normal infant had a mean value of 3.4% at birth, after which there was a rapid drop during the first month to 0.16% with a standard deviation of 0.12%. This they regarded as normal throughout the first year. Blood platelets at birth were found to have a mean value of 227,000. After a rise at the third month, their mean value throughout the remainder of the first year was 344,000 with a standard deviation of 66,000.

The leukocytes vary considerably. This is true especially in the neonatal period. Kato[2] made 1081 total and differential leukocyte counts on 1037 individuals ranging in age from birth to 15 years. He found that the total leukocyte count was very high during the first 2 days with a maximum averaging 22,000 at the end of the first 24 hours of life. There was a sudden pronounced drop in the count on the third or fourth day, averaging 8750. During the first 3 months there was a slight temporary rise up to an average of 10,000 to 11,000. After this the normal level averaging 8000 was maintained, although there was a tendency to a gradual fall throughout the remaining period of infancy and childhood. The total granulocytes (neutrophils, eosinophils and basophils) were correspondingly high during the first 3 days of life. They fell sharply on the fourth day of life, paralleling a similar sudden drop of the total leukocytes. From 3 weeks to 4 years the total number of granulocytes was much lower in both relative and absolute numbers than that of the lymphocytes. Eosinophils and basophils were found constantly throughout childhood, but no significant variations were observed in normal children. The total lymphocytes were relatively low at birth and dropped sharply on the third day, but rose rapidly to reach their highest peak during the second month. After this the lymphocytes were greater in number than the granulocytes, until the fourth year when the two cell types were equally distributed. After the fifth year the lymphocytes decreased steadily until the fifteenth year when they were about one-half as numerous as the granulocytes. The monocytes were present in large numbers in the neonatal period. After 2 weeks, the number of monocytes fell to a level which was maintained throughout childhood. The lymphocytes and the monocytes seemed to bear a quantitative relationship to each other, a ratio being obtained by dividing the percentage of monocytes by that of the lymphocytes. This monocyte-lymphocytic ratio described a definite curve of variations from infancy to childhood. A similar ratio was observed between lymphocytes and granulocytes. It was caclulated by dividing the percentage of the total granulocytes by that of the lymphocytes. These two ratio curves are somewhat identical in nature, the only difference being that the actual value of the granulolymphocytic ratio is approximately 10 times greater than that of the monocyte-lymphocytic ratio.

Washburn[3] attempted to discover what variations of leukocytes were present in normal healthy infants during the first 3 months of life. His observations covered hourly fluctuations on different days in the same babies. He found that the total leukocyte counts varied between 4000 and 23,000 per cmm. without indicating the presence of any demonstrable disease process. The leukocyte counts in any individual baby tended to fluctuate within a definite zone, but this zone was not the same for every baby of a given age and size. There was no evidence of orderly rhythm in the fluctuations of the leukocyte count during the hours of the day or night. There is no reason for expecting counts done at the same hour on different days to be comparable. He was unable to show any relationship between the number of leukocytes and such factors as the intake of food, digestion, sleep, increased activity or minor external disturbances. He found that the

lymphocyte was the cell type that was responsible for the sharp fluctuations in total white cell count.

Considering the types of leukocytes, one is impressed with the lack of uniformity in classifying white cells in textbooks and in the less recent literature. A Renaissance of interest in the blood dyscrasias has stimulated research into the elements of the blood in healthy individuals as well as in sick people. One vitally important development has been the attempt to classify the types of leukocytes. Washburn[4] points out that there is no great difficulty in classifying eosinophils and basophils because of the typical stain reactions of the granules. The neutrophils have been divided into myelocytes, immature and mature polymorphonuclears. The mature cell shows in its typical form a well segmented nucleus of from 2 to 6 lobules joined by narrow bands of nuclear material and with its neutrophilic granular cytoplasm. The immature cell is usually slightly larger and its nucleus is unsegmented, though it may be somewhat lobulated. It is plump and somewhat vesicular in appearance and presents a shape which varies from a shallow U or irregular S to that of a rather slender kidney. This group corresponds most closely to Schilling's juvenile cell and may include a few cells which he would classify as stab cells. The myelocyte is usually fairly characteristic, being approximately the same size as the immature polymorphonuclear, with a round or plump kidney-shaped nucleus and with distinctly more tendency to a basophilic reaction in the granular cytoplasm. The only cell with which it might be confused is a monocyte that is unusually granular. The still more immature promyelocyte and myeloblast are found in the circulation, chiefly in leukemia.

The lymphocytes are the predominant white cells in the blood of the infant for the greater part of the first 6 months of life. They differ from lymphocytes in the blood of adults not only in numbers but also in the type of cell. The typical small lymphocyte of the adult blood or of that of older children is not the most characteristic of the group in infancy, where they seem to be divided equally into large and small types. There is, however, a large proportion of lymphocytes intermediate in size between the real small lymphocytes of the adult and the definitely large type of infancy, which measures 2 or 3 times the diameter of the erythrocyte.

The monocytes form a large heterogeneous group. The typical monocyte is slightly larger than a mature neutrophil and has a slate-gray background containing fine pinkish staining granules which tend to occur in groups. Its nucleus is large and roughly kidney-shaped and stains a paler purple than that of either the lymphocyte or the mature neutrophil; the chromatin is more finally divided. Less than half of the monocytes in the blood of young infants belong to this type. About an equal number show varying amounts of coarse granulation, usually purplish and sometimes, but not always, obscuring the characteristic cytoplasm. The nuclei of these cells are often more deeply stained, and present almost every shape from a round or slightly indented to a truly segmented form with two distinct lobes. This type of monocyte may be difficult to differentiate from the myelocyte or immature neutrophil; but in most cases the characteristic gray cytoplasm and pinkish granulation of the monocyte can be recognized.

Agranular forms of monocytes are seen occasionally, with a more bluish cytoplasm that may contain a very few fine granules. The nucleus may be round, kidney-shaped or actually bilobed. In the blood of the same infant every variation from the agranular to the typical monocyte and from the typical to the very granular form may be seen.

There are cells which are definitely less mature than a myelocyte or than a very large lymphocyte. These have been called blast cells. There has been no attempt to divide them into lymphoblasts, myeloblasts, or monoblasts. These show a very deep blue agranular but fuzzy cytoplasm with a large round or oval nucleus which may be eccentric. Their diameter varies from 2 to 5 times that of a red cell. There is also considerable difference in the compactness of chromatin in the nucleus, although the nuclei of all of these cells stain deeply. The nucleus may appear as an almost solid mass as arranged in whorls or like a solid mass that has been fractured in many places. This last type resembles a megaloblast. The blast cells are not seen as often in the neonatal period as between the fourth and eighth weeks.

From 0.5 to 2% of the leukocytes may resist classification. These are mostly mononuclear forms and probably represent a heterogeneous group of atypical cells, some of which are immature and some degenerate forms, although from their appearance they may seem to be whole functioning cells. According to Washburn in childhood the lymphocytes vary from 27 to 88%; neutrophils, from 5 to 63; all granulocytes, from 10 to 68 and monocytes from 1 to 18%.

According to the Schilling classification there are 3 main divisions of white blood cells; granulocytes, monocytes and lymphocytes. Roughly speaking, an increase of granulocytes is noted in acute infection, of monocytes in subacute infection and of lymphocytes in chronic infection. The change in granulocytes, especially in neutrophils, in acute infection is the main factor in interpreting blood smears by the Schilling classification. He subdivides the neutrophilic granulocytes into 4 groups; segmented or mature forms; stab, staff, band or nearly mature forms; juvenile or immature forms; and the myelocyte or the least mature form of all. An increase in the immature forms is spoken of as a shift to the left. The nucleus of segmented neutrophils is subdivided into two or more parts which are joined by pyknotic filaments. In stab cells there is a more or less continuous nucleus with heavy chromatin areas in it and a nucleus in the shape of an S, T, U, V, W or Y. Juveniles are neutrophils with a continuous nucleus normally shaped like an U or kidney or peanut. There are no dark chromatin masses, but there may be a nucleolus in each terminal. In addition the nucleus of juveniles is paler, broader and usually ends in club-like extremities and occasionally the cytoplasm has a pale bluish cast. Myelocytes have a single round or oval nucleus, and their cytoplasm stains distinctly blue with large pink granules in it. An arrangement of the leukocytes in a horizontal line, basophils, eosinophils, myelocytes, juveniles, stab, segments, lymphocytes and monocytes with their percentages presents the Schilling hemogram. An increase of the immature granulocytes (*i. e.*, those to the left) constitutes a shift to the left and indicates an increase in infection. When stabs with prominent irregular granules are increased with an associated decrease of the segments the shift is spoken of as a degenerative one. It represents an interruption in the

developmental phase of neutrophils by a toxic impression on the bone marrow. With a stimulation of the regenerative process of the bone marrow by severe toxins, more new cells are formed in a "regenerative shift," which is seen only in severe infections. Both degenerative and regenerative shifts may go on simultaneously.

The chief abnormal varieties of leukocytes in the peripheral blood are metamyelocytes, neutrophilic myelocytes, myeloblasts and lymphoblasts. The metamyelocytes are the connecting links between the myelocytes of the bone marrow and neutrophils of the blood. The nucleus is indented and the cell is usually smaller than the myeloblast and the myelocyte, being about the size of the mature neutrophil, which it resembles in every way except in the shape of the nucleus. The metamyelocytes may be subdivided into two types; those with a slightly indented nucleus which are called young or Y type, and those with a deeply indented nucleus which are called band or B type. The neutrophilic myelocytes are the bone-marrow precursors of the neutrophil in the normal blood. All 3 of these forms of myelocytes, especially the neutrophilic, are found in the blood stream in the severe infections with extensive leukocytosis, but they are only seen in large numbers in splenomyelogenous leukemia. They are all developed from myeloblast as large mononuclear cells, whose protoplasm is filled with neutrophilic, eosinophilic or basophilic granules. The nucleus occupies most of the cell and is round, oval or slightly indented. The granules do not as a rule stain as deeply as similar granules in normal cells of the blood. Myeloblasts, the parent cells of the myelocytes are met in acute myelogenous leukemia and in the terminal stages of chronic myelogenous leukemia when the bone marrow reverts to the embryonic type. They do not have granules. The nuclei are round or oval and poor in chromatin with pale blue nucleoli. Lymphoblasts occurring in acute lymphatic leukemia, are large cells closely resembling the large or immature lymphocytes of normal blood, especially in children. Deep blue granules are sometimes seen in the cytoplasm, and the nucleus shows usually one or two nucleoli. At times the nucleus may be lobulated and is termed the "Rieder cell." The nucleus may be lobulated also in myeloblasts.

Nussbaum[5] endorsed the application of the Schilling method of study of the blood as a valuable aid in diagnosing the presence of infection in pediatric cases. From a study of 432 hemograms of 232 children he found that the chief change in the hemogram in the presence of active infection was the increase in the percentage of immature neutrophils in the peripheral circulation. According to the percentage of immature granulocytes (stabs, juveniles, myelocytes and myeloblasts) present in the peripheral blood, cases may be grouped into 5 classes: no regenerative shift (less than 10%); mild regenerative shift (10 to 20%); moderate regenerative shift (20 to 35%); marked regenerative shift (above 35%), and marked regenerative shift with signs of exhaustion of the bone marrow when more than 10% of myeloblasts, myelocytes and juvenile cells are present. The degree of regenerative shift is proportional to the virulence of the invading organism except for slight individual variation.

Osgood and Baker,[6] studying 112 healthy boys and 103 healthy girls between the ages of 4 and 14 years found no significant differences

on the basis of age and sex. The normal ranges for children of these ages were found to be as follows: red blood cells, 4,200,000 to 5,800,000; hemoglobin, 10 to 14 gm.; hemoglobin coefficient, 10.20 to 13.80; cell volume, 31 to 41 cc.; color index, 0.85 to 1.15; volume index, 0.85 to 1.15; saturation index, 0.90 to 1.10. These observers class as anemic those children with erythrocytes below 4,200,000 or the hemoglobin below 10 gm., or both. A diagnosis of "secondary anemia" is decried as it does not indicate the type of anemia, the etiology, or the treatment. In macrocytic anemia the color and volume indexes are above 1.15 and the saturation index is normal. This type responds to treatment with the active principles of the liver or of the stomach. Normocytic and simple microcytic anemias show normal or low color and volume indexes and a normal saturation index. The treatment of these types is the removal of the cause. Transfusions are of benefit sometimes, but liver and iron do not help. Microcytic hypochromic anemia shows color and volume indexes below 0.85 and a saturation index below 0.90. The cause of this type is usually chronic hemorrhage, deficiency of iron in the diet or achlorhydria resulting in deficient absorption of iron. Iron in large doses, especially in the form of ferrous sulphate acts usually as a specific.

The majority of premature and immature babies either present a more or less severe anemia at birth, or it develops soon thereafter. This fact was corroborated by the observations of Merritt and Davidson.[7] The anemia in immature babies is less marked usually than that in premature infants. Josephs[8] has attempted to determine the mechanism of the physiologic anemia of prematurity. As regards the response of reticulocytes, and its relation to the administration of iron he found that there was no basis for the idea that the fall in red cells and hemoglobin was dependent on hypoplasia. During the first 6 to 10 weeks after birth administration of iron resulted in no improvement. The length of the period was in direct ratio to the degree of prematurity. After an early period of non-reactivity, there followed a short transitional period with delayed response, after which administration of iron was followed by a prompt response in the reticulocytes and a rise in red cells and hemoglobin. He could find no evidence to show that the lack of stores of iron plays any part in the development of or in the persistence of the anemia before the end of the third month; but after that time the rise in the red cells without a corresponding rise in the hemoglobin in untreated infants indicates that lack of stored iron has become an important factor. He was not convinced that a low percentage of hemoglobin was in itself harmful, although he thinks that it is indicative of a condition that renders the infant more susceptible to infection. Although iron may raise the hemoglobin content, transfusion is recommended as the method of choice in treating the condition as a whole. Abt[9] found the change in oxygen tension, the increased hemolysis after birth, the fragile and immature red cells and the embryonal type of hemoglobin in the premature as well as in the full term new-born infant. In addition the premature baby has a smaller total blood volume, and the increment in growth was greater, and with the rapid gain in weight and growth there must be a corresponding increase in the blood volume. As a consequence the demand for new blood formation in the premature is much greater. There is no way of measur-

ing accurately the efficiency of the formation of blood, but it is a logical assumption that the immature blood-forming organs of premature infants are not capable of supplying fully the demands of the rapidly growing premature infants in the first 8 to 12 weeks after birth. This incapacity is comparable to the imperfect functioning of the gastro-intestinal, the cardiovascular and heat-regulating systems in these babies.

At best the classifications of anemias are not very satisfactory in either adults or children. The leukemias constitute a fairly well-defined group. The characteristic of these is a great overproduction of leukocytes associated with an anemia. At times there is a failure of the leukocytes to increase for a part of the illness. In such cases this is known as an aleukemic phase, and it gives rise to considerable difficulty in diagnosis. In fact diagnosis may be impossible unless other factors indicate the correct conclusion. According to Parsons and Smallwood,[10] exclusive of the leukemias, the anemias of infancy and childhood may be divided into two main groups; the hypoplastic, anhematopoietic or deficiency anemias, and the hemolytic or erythronoclastic anemias. The first group is characterized by defective blood formation, either a qualitative or quantitative failure which is the result frequently of nutritional disturbance such as iron starvation in the nutritional anemia of infancy and the hypochromic anemia of coeliac disease or the vitamin deficiency in the anemia of scurvy. The second group is characterized by excessive destruction of the circulating blood cells, perhaps associated with damage of their precursors in the bone marrow. The damage to the bone marrow may paralyze either temporarily or permanently its blood-forming activities, *i. e.*, aplasia.

Abt[11] classified blood dyscrasia of infancy and childhood into two groups, depending on whether leukocytosis or leukopenia was present. His group with leukocytosis he subdivided into two subgroups; non-leukemic conditions simulating leukemia and leukemias simulating other conditions. Examples of the non-leukemic conditions simulating leukemia are pertussis, pneumonia, sepsis, von Jaksch's pseudoleukemic anemia. Cooley's erythroblastic anemia, infectious mononucleosis, mediastinal tumor and Niemann-Pick's essential lipoid histiocytosis. In leukemia simulating other conditions it is possible for a leukemia to be present at the same time as other conditions so that the manifestations of the other diseases may overshadow the signs of the leukemia. As examples of this are found leukemia associated with mediastinal tumor, rheumatism, diarrhea and parotitis. In the classification of blood dyscrasias with leukopenia there are also two groups: non-leukemic conditions simulating leukemia and aleukemic leukemia simulating other conditions. Under the first heading are grouped sepsis, agranulocytosis, Gaucher's disease, aplastic anemia and malaria. Under the second heading sepsis, appendicitis and aplastic anemia must be considered. Hodgkin's disease was not included by Abt, but according to Smith,[12] who studied 20 children with this disease, they showed a progressive anemia and a tendency to leukopenia with an increase of monocytes.

The many dycrasias of the blood in infancy and childhood cannot be given adequate consideration here. In fact many can only be enumerated as in the classifications given above. Unfortunately these classifications do not include all types of diseases presenting abnormal blood pictures

that are encountered in childhood. Among those not listed already are pernicious anemia and purpura. Several of those listed in Abt's classification demand more specific consideration.

Givan and Shapiro[13] analyzed 29 cases of symptomatic agranulocytosis and a reported case of their own. Although the cause of this pathologic condition is not known definitely, the frequency with which it is associated with severe antecedent infection must be regarded as more than a casual relationship. The disease has been described as a granulopoietic disease of the bone marrow. In the particular case cited adenin sulphate was used as a stimulant. With the reappearance of the granular elements the blood stream infection was overcome, the blood picture became normal and surgery was successful in clearing out infected areas in the jaw with the ultimate recovery of the patient.

Greenwald[14] says that aplastic anemia is characterized by its rapidly and progressively fatal course. The two outstanding features are the anemia and the hemorrhagic diathesis, which manifests itself by hemoptysis, epistaxis and purpuric eruptions. Fever is usually present throughout the disease. Pigmentation of the skin may be present. There are always cachexia and weakness. Sometimes necrotic areas develop in the mucosa of the mouth. The blood picture is the chief feature in diagnosis. There is a decrease of hemoglobin to 10 to 15% and the erythrocytes may be 1,000,000 or less. The color index is approximately 1. Nucleated red cells are usually absent although monoblasts may be met. Reticulocytes and polychromatophilic erythrocytes are absent. There is a leukopenia with a marked reduction of neutrophils and an almost complete absence of eosinophils. There is a marked increase in the lymphocytes.

Cohen[15] believes that congenital anemia of the newborn and erythroblastosis are not synonymous, and reports a case of anemia of the newborn without erythroblastosis in support of his claim. However, these two conditions often occur together. Andrews and Miller[16] report 4 cases of anemia of the newborn showing erythroblastosis; Brown, Morrison and Meyer[17] report a case without erythroblastosis. At autopsy a careful search of all tissues available for study failed to reveal the degree of extramedullary hematopoiesis characteristic of erythroblastosis.

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PHYSIOLOGY

PROCEEDINGS OF

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SESSION OF NOVEMBER 18, 1935

A Study of the Average Temperature of the Tissues, of Heat Exchange and Vasomotor Response to Temperature by Means of a Bath Calorimeter.—A. C. BURTON and H. C. BAZETT (Laboratory of Physiology, University of Pennsylvania). A well-stirred "bath tub" was kept at constant temperature by a mercury-toluol regulator which periodically switched on an electrical immersion heater. A device using a self-starting synchronous motor (telechron) recorded the time the heater was "on" in any period of elapsed time. A subject was immersed to the neck and the bath was sealed by a layer of paraffin wax. Comparison was made with control periods without the subject, and this enabled the heat given by the subject to the bath to be calculated. Rectal temperatures were electrically recorded continuously and oxygen consumption was measured by a Sanborn machine. Thermocouple measurements showed that the temperature of the surface of the body was within 0.1° C. of that indicated by the bath thermometer. Loss of heat from the head to the room was less than 10% of the total loss.

Experiments with 16 different bath temperatures between 30° C. and 36° C. on one male subject showed:

1. When the surface temperature changes by more than 1° C., the resulting changes in rectal temperature are totally inadequate to indicate the heat gained or lost by change of average body temperature, as measured by the calorimeter. A much better estimate was given by using the formula (previously developed by one of the authors):

$$\text{Average temp.} = 0.65 \times \text{rectal temp.} + 0.35 \times \text{surface temp.}$$

2. The heat production is better correlated with this average temperature than with the rectal temperature. There is a minimal metabolic rate in baths in which there are no hot or cold sensations.

3. Raising the bath temperature by large amounts (greater than 2° C.) leads to a temporarily reversed gradient in the superficial tissues,

with heat passing from bath to subject. The response of the rectal temperature to changes of bath temperature is greatly delayed and, when these changes are moderate, initial paradoxical changes of rectal temperature may occur. These are explained, with reference to a physical model, as due to reflex vasomotor changes in the effective thermal conductivity of the tissues.

4. These vasomotor changes are able to keep the heat loss to the bath in the normal range when the difference between rectal temperature and bath temperature varies between 1° C. and 4° C. A greater difference entails increased loss and the stimulation of increased heat production. The constancy of the heat loss is achieved by a change of the effective thermal conductivity of the tissues by a factor of about 5 times.

5. An increase in thermal conductivity is observed with temperature differences exceeding 4° C.; this develops with the onset of increased heat production. It depends, probably, on an increased blood flow to muscles, rather than on any skin hyperemia.

Experiments on a second male subject gave concordant results, while those on a female subject showed considerable divergence.

Further Studies on the Mechanism of Hypertension Following Intracisternal Injection of Kaolin.—M. A. LINDAUER, W. A. JEFFERS, and J. Q. GRIFFITH (Robinette Foundation, University of Pennsylvania). Six rats, made hypertensive by subtotal nephrectomy, were given 0.05 mg. of ergotamin tartrate per 100 gm. of rat intraperitoneally. The results were inconstant. On the other hand, 13 rats, made hypertensive by intracisternal injection of kaolin and given the same dose of ergotamin tartrate, all showed rather marked initial falls in blood pressure, although some came back to their former level or even higher in a very short time.

The carotid sinus reflex behaves in a normal manner in rats made hypertensive by the intracisternal injection of kaolin, *i. e.*, stimulation of the carotid sinus leads to a fall in blood pressure.

The removal of circulating adrenalin from the blood stream by a right adrenalectomy and left splanchnic nerve section with enucleation of the left medulla causes a transient fall in blood pressure, but this fall is of the same order of magnitude as that seen in normal animals that have been trated in the same way.

The Nature of Cell Permeability to Ammonium Salts.—M. H. JACOBS (Marine Biological Laboratory, Woods Hole, and Laboratory of Physiology, University of Pennsylvania). It has been shown by Ørskov that the rate of osmotic hemolysis of erythrocytes exposed to NH_4Cl solutions is enormously accelerated by the addition of small quantities of bicarbonates. It is believed by him that undissociated CO_2 cannot be an important factor in producing this effect, because, among other reasons, of the fact that certain other weak acids, of which boric acid is the clearest example, do not behave similarly. It can, however, be shown theoretically that not all weak acids could be expected to have this effect; boric acid happens to be a particularly unfavorable one. A much more suitable acid would be H_2S, which in the magnitude of its dissociation constant and in the ability of its undissociated molecules to enter cells readily closely resembles carbonic

acid. It has been found that Na_2S does, in fact, approach $NaHCO_3$ in its effectiveness in accelerating hemolysis by NH_4Cl; control experiments indicate that the formation of sulph-hemoglobin is not an important factor in producing this result. It has also been found that NH_4 benzoate and NH_4 salicylate have a remarkable power of reversibly inhibiting hemolysis by NH_4 salts of strong acids, in which presumably penetration of the cell by anions is involved, but that this effect is lacking in the case of the NH_4 salts of weak acids and in that of non-electrolytes. The fact that the bicarbonate effect on NH_4Cl hemolysis is not inhibited by the presence of benzoates and salicylates is perhaps further evidence of its essentially molecular nature.

Relative Biologic Effectiveness of Roentgen Rays and Neutron Rays.—R. E. ZIRKLE (Eldridge R. Johnson Foundation, University of Pennsylvania). Recent developments in atomic physics, notably the discoveries of the neutron and of artificial radioactivity, promise to furnish powerful methods in biology and medicine.

Experiments with neutrons (speedy, uncharged particles of mass equal to that of the ordinary hydrogen atom) have been carried out in the Radiation Laboratory, University of California, Prof. E. O. Lawrence, Director. One Roentgen (air ionization unit) of neutrons was found to be equivalent to 20 Roentgens of Roentgen rays in retarding growth in wheat seedlings. This difference in action between Roentgen rays and neutrons indicates an imperative need for a direct and complete investigation of neutrons as a technique for tumor therapy.

The elements which can be made radioactive include many which are normal constituents of living matter. These promise to become valuable tools in following the movement and metabolism of substances in biologic systems.

Nuclear chemistry, a whole new field dealing with the reactions of atomic nuclei, offers new methods of qualitative and quantitative analysis. The nuclear reactions of some elements are more characteristic and easier to measure than the ordinary, or electronic, reactions.

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ORIGINAL ARTICLES.

THE SIGNIFICANCE OF NORMAL AND MORBID FORMATION AND DISTRIBUTION OF CELLULAR AND NON-CELLULAR CONSTITUENTS OF BLOOD AND LYMPH.*

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The identical objectives of medical workers, whatever be their laboratory and clinical endeavors, are to acquire and to apply knowledge needed to improve, devise and to utilize therapeutic methods that will minimize disabilities and thus prolong active life. Objectives can be attained by assisting people to develop, conserve and transmit to offspring the capacity to produce life-sustaining, health-maintaining and health-regaining groups of functions. Means to attainment are indicated through realization that the efficacy of each group of these fundamental functions depends upon production, equable and economic distribution of an adequate volume of blood and lymph of requisite quality.

Consequently, the methods assuring the utmost efficacy in prevention and treatment of antigenic and non-antigenic diseases are ultimately disclosed by hemology, which includes hemo-lympho-plasmology and hemo-lympho-cytology; *i. e.*, the structure, functions and modes of production and storage of each non-cellular and cellular constituent of blood and lymph and knowledge of activities responsible for wholesome and unwholesome modes of distribution of blood and lymph. Information needed to select and adroitly to utilize appropriate measures is derived from all sources—personal and

* Address of Chairman, Section of Abdominal and General Surgery, American Medical Association, Atlantic City, N. J., June 12, 1935.

family history, every manner of examination, clinical experience, etc., which will not be here discussed—but more particularly from normal and morbid physiology.

Normal physiology has shown that blood and lymph form the internal environment of a body (Bernard) which is separated from tissues by endothelial lining of cardiovascular walls. Balance in, among (Bernard, 1869) and between (Hewson, 1774) the cellular and non-cellular constituents of blood and lymph, together with balance (equity) in the distribution thereof, is requisite to health. The cellular and non-cellular constituents of the internal environment fluctuate qualitatively and quantitatively with alterations in living conditions and the total volume of blood in more or less active circulation, volumes distributed to divers structures at varying velocities and expenditures of cardiac energy likewise fluctuate with living conditions. Healthful balance in, among and between constituents, balance in total and unit volumes of blood and an economic distribution are conserved by automatic adjustments (Cannon). Automatic adjustments are pressor and depressor influences that so regulate hemopoietic and cardiovascular activities as to restrain fluctuations in formation and delivery of internal environment within upper and lower healthful limits. Consequently, all balances fluctuate between high (favorable) and low (unfavorable) limits, and life-sustaining functions produced when balances are favorable have a wider margin of safety, when balances are unfavorable, a narrower margin of safety. The duration of production of life-sustaining functions depends upon the inherent competence of hemopoietic cells, cardiovascular cells and the cells effecting automatic adjustments and upon the exertion-rest intervals of their experiences.

Morbid physiology has disclosed an almost incessant subjection of individuals to actions of pathogenic influences from conception until death. Unchecked pathogenic influences first reduce favorable to unfavorable balance in production or in distribution of constituents of blood and lymph, or both, then convert an unfavorable balance that is incompatible with disease into an imbalance that is incompatible with health and finally increase the imbalance until it becomes incompatible with life. Pathogenic influences awaken additional automatic adjustments (resistance, defense and repair) which tend to check them. If these adjustments are more or less effective they conserve favorable or unfavorable balances (health-maintaining functions); if ineffective for shorter or longer intervals and then become effective, they convert imbalance (disease) into balance (health-regaining functions); if persistently less ineffective, they protract; if more ineffective, they fail to protract production of life-sustaining functions.

Antigenic influences, exerted from establishment of a fetal circulation until death, are the entrance into internal environment from

tissue or from external environment (maternal circulation in fetus) or irritating cellular constituents and viruses (parasites) or non-cellular constituents (foreign proteins; *i. e.*, parasitic and non-parasitic antigens) which are, despite filtration by vascular endothelium, lymph glands, lungs, liver, spleen, bone marrow and kidneys, rapidly disseminated in some measure throughout the body. Automatic adjustments aroused by antigenic influences are local, intermediate and systemic responses. Local responses are evoked by irritation of tissue into which parasites are primarily implanted and in which antigens are primarily diffused. Intermediate responses are caused by irritation of vascular endothelium through which parasites and antigens pass into lymph and blood, the divers lymph and blood filters through which the lymph and blood flow and the vascular endothelium through which parasites and antigens pass from the lymph and blood to enter vascular walls and perivascular tissues. Systemic responses are occasioned by irritation of tissues by parasites and antigens that have passed into them through vascular walls. Automatic adjustments produce and introduce into the internal environment counterirritating cellular (increased leukocytes) and non-cellular (antibody) constituents which are rapidly disseminated and delivered through vascular walls into tissues containing parasites and antigens. If these adjustments are effective, they inactivate or destroy parasites and neutralize antigens promptly (health-maintaining functions) or after an interval of illness (health-regaining functions). If less ineffective, they protract, if more ineffective, fail to protract, production of life-sustaining functions. A continuous presence of antigens in and the repeated entrance of parasites into the internal environment necessitates an equally continuous formation of increased numbers of appropriate forms of leukocytes and an elaboration of antibodies. Thus the divers cells productive of health-maintaining and health-regaining functions requisite to survival are kept, so long as not incapacitated, in the state of active preparedness required to provide resistance and defense against the inevitably recurring more or less potent antigenic irritations.

Hemopoietic and cardiovascular cells and those productive of automatic adjustments (pressor and depressor nerve impulses, hormones, etc.) inherit strength or weakness and are beset from conception until death with non-antigenic influences; namely, the wear of usual, the tear of unusual modes of living, actions of non-antigenic irritants, etc., which, together with antigenic influences, determine the duration of cellular competence. Incompetence of these groups of cells to which antigenic influences may contribute can introduce fluctuations in their activities that exceed upper and lower healthful limits; *e. g.*, polycytoses or cytopenias, hyper- or hypoglycemia, hyper- or hypothyroxinemia, mental and nervous instability, inequable (Raynaud's) and uneconomic (hypertension)

distribution of unit and gross volumes of blood. Automatic adjustments aroused by non-antigenic influences consist of compensatory and adaptive alterations in structure and function of some cells to offset subcompetence in others. If the adjustments are immediately effective, they conserve balance (health-maintaining functions); if later they become effective, they restore balance (health-regaining functions); if persistently less ineffective, they protract, if more ineffective, fail to protract production of life-sustaining functions. The wear of usual modes, the restricted stress of less unusal modes of living and of milder irritations provide exercise whereby all but frail cells acquire strength so that non-antigenic influences tend to conserve and to raise the competence of cells productive of life-sustaining, health-maintaining and health-regaining functions. Antigenic influences can introduce non-antigenic diseases and *vice versa*, so combinations of both forms of disease are not infrequent.

Means to attainment of therapeutic objectives through coördinated laboratory and clinical efforts are indicated by normal and morbid physiology and experience. They are to establish hemologic data from repeated detailed examinations of the constituents of the internal environment and of the modes of their distribution and *to interpret these data in conjunction with all other information.*

The requisite data will answer the following questions:

Is there balance or imbalance in either blood and lymph formation or circulation, or both?

Prevention. Is any balance revealed by mean level of inevitable fluctuations favorable or unfavorable? If a balance is favorable, what measures will conserve it and thus continue insusceptibility by protecting the competence of cells productive of life-sustaining, health-maintaining and health-regaining functions? If a balance is unfavorable, is it regressing, stationary or progressing? Is reduction from favorable to unfavorable balance attributable to actions of antigenic, non-antigenic influences or both? How can pathogenic influences be eliminated without imposing additional handicaps? If an unfavorable balance is regressing, how can the person be assisted to regain and maintain a favorable balance? If stationary, how can regression be introduced and promoted? If progressing, how can an increasing unfavorable balance be arrested before it has exceeded healthful limits (susceptibility), regression be introduced and promoted? Repeated examinations furnish data that will determine whether the measures as they are being employed are efficacious or inefficacious, how they should be modified, how long they should be continued and when they should be reintroduced.

Treatment. Is the mean level of any imbalance high or low, acute or chronic, regressing, stationary or progressing? Is an imbalance attributable to actions of antigenic, non-antigenic or to both influences and how can pathogenic influences be eliminated

or reduced without adding more than transiently and immaterially, if at all, to existing burdens? If an imbalance is regressing, how can an individual be assisted to regain balance (recovery), to reëstablish (acquired insusceptibility) and to maintain a favorable balance (acquired immunity)? If stationary, how can regression of an imbalance be inaugurated and facilitated? If progressing, how can an imbalance be arrested before it has exceeded recoverable or viable limits and regression be introduced and fostered? Repeated examinations will furnish data that will indicate the efficacy or inefficacy of measures as they are being employed, suggest modifications or other methods, the duration of beneficial employment and when reëmployment will obviate recrudescence.

We must recognize our obligations to assist people to acquire and to conserve favorable balances or to regain and to maintain the most favorable or least unfavorable balances or imbalances circumstances permit. Satisfaction of those obligations demands not only the timely utilization of appropriate non-operative and also frequently of operative measures of established efficacy, but also the extension of this effort as information increases. It is not pertinent here to try to summarize actual and potential accomplishments with available knowledge and measures nor to attempt to suggest lines of endeavor that would widen the scope of accomplishments. If we realize that immunologic part of morbid physiology defines means to combat antigenic influences and morbid physiology discloses methods to combat non-antigenic influences, we can find dependable therapeutic indications from limited knowledge of and investigative indications from ignorance of (1) cellular; (2) non-cellular; (3) both cellular and non-cellular constituents; (4) the distribution of (5) and storage of both with provision of margins of safety.

1. What are the numbers and functions in health and disease of each variety of corpuscle and of platelets and what are the favorable and unfavorable influences that govern their production? What is the competence of these corpuscles and of the cells producing them as revealed by numbers and by proportions of immature, mature and senile forms? What are the inter-relationships shown by monocyte-lymphocyte, large lymphocyte-small lymphocyte, monocyte-neutrophil, eosinophil-neutrophil, and basophil-neutrophil ratios? Do the numbers, proportions and ratios indicate a favorable balance, an approaching or existing imbalance? What is the existing degree of competence or grade of incompetence of hemocytoblasts and how can their welfare be best served according as an active pathogenic influence be antigenic or non-antigenic? (Hemology has been dominated overlong by hemocytology, indeed by hemocytomorphology, just as pathology has been subjected to the benumbing influence of morbid anatomy. Valuable as is knowledge of alterations in numbers, proportion and ratios of corpuscles,

there are other alterations in the entire blood that are too frequently ignored and often furnish even more significant information.)

2. What is the volume of each constituent of blood plasma and lymph (water, proteins, carbohydrates, electrolytes, vitamins, hormones, chemical intermediaries in transmission of nerve impulses, anabolic and catabolic products, antigens, antibodies, etc.)? What are the relationships or ratios between the constituents; *e. g.*, water and solids, albumins and globulins, divers salts, carbohydrates, vitamins, fats and pressor and depressor hormones and intermediaries of nerve impulses, antigens and antibodies, etc.? Do the volumes, physicochemical attributes and ratios indicate a favorable balance, an approaching or existing imbalance? What is the competence or incompetence of cells producing non-cellular constituents? How can those cells be protected or their rehabilitation be promoted if the pathogenic influences are antigenic or non-antigenic? (Great as has been the advance in knowledge of the constituents of lymph and plasma, it is little more than introductory.)

3. What is the concentration of the plasma? Does it provide the wholesome degree of viscosity (normal sedimentation rate) requisite to appropriate distribution with optimum expenditure of cardiac effort? Is concentration of plasma raised (retarded sedimentation rate) or lowered (accelerated sedimentation rate)? Is sedimentation unduly retarded because of disproportionate increase in corpuscles (polycythemia vera)? Is it healthfully retarded by an unusual surplus of antibodies effecting a favorable balance in antigen-antibody ratio? Is sedimentation unduly hastened because an excess of antigenic irritants unneutralized by antibodies or a surplus of non-antigenic irritants present in the plasma have effected a withdrawal of water from tissues to dilute them and promote their elimination? (Hastened sedimentation caused by excess of unneutralized bacterial antigens was noted by Hewson, in 1774, as an increased buffy coat on surface of blood clots after phlebotomy. Accelerated sedimentation if provoked by presence of non-parasitic foreign proteins in plasma can be estimated as urticaria develops. Francis D. Murphy has observed the development of hastened sedimentation with rise of N.P.N. because of acute nephritis and of slowing of sedimentation as renal lesions subside. Obstructive jaundice introduces an irritating excess of bile salts into blood and hastens sedimentation. Hemolytic jaundice does not introduce such irritation and sedimentation is not accelerated, may even be retarded.)

4. Is equable distribution in healthful states associated with homogeneous mixture of constituents of plasma and homogeneous distribution of corpuscles in plasma whether circulation is more or less rapid? When there is inflammation, are appropriate leukocytes drawn to the periphery of the plasma in smaller vessels as a first

stage in migration by chemotropism of antigenic and non-antigenic (fibrin) irritants in the tissues? Are platelets similarly drawn to the periphery of plasma in vascular injury or inflammation? What cardiovascular and vasomotor states conserve and disturb the homogeneity of mixture and the usual proportions of all constituents of internal environment? Are such anomalies the cause or consequence of inequable distribution and if so, how are they correctable? Is arteriolar constriction the ultimate cause of essential hypertension? Does the constriction affect all arterioles or is it sometimes more pronounced in splanchnic vessels, sometimes in the systemic? If this explains why divers methods of treatment are dissimilarly efficacious, how can the distribution of constriction be recognized? (Efforts now being made to correct inequable and uneconomic distribution will eventually disclose the causes and establish prophylaxis.)

5. What are the extravascular and intravascular sites of storage for surplus cellular and non-cellular constituents? What influences regulate the storage of surplus constituents and withdrawals from storage of constituents needed to preserve balances? How can margins of safety be protected against shortages? When should potential shortages be prevented or actual shortages be covered by intravenous introduction of unmodified whole blood or of certain constituents; *e. g.*, salt, sugar? (Antibodies, because some forms of parasitic or non-parasitic antigens are ever present in tissues and in internal environment, are quite the most potent single contribution to health-maintaining and regaining functions upon which survival depends. All cells are repeatedly subjected to actions of antigens, virtually all cells elaborate antibodies, particularly the reticuloendothelium in lymph and blood filters. Surplus antibodies are distributed in lymph and blood and stored in tissues most liable to invasion by parasites, to infiltration by antigens (*e. g.*, skin and subcutaneous fat, mucosæ and submucosæ, serosæ and subserosæ, fascia delimitating regions and vascular endothelium) and in tissues harboring parasites. So long as antigen-antibody balance obtains, the numbers, proportions and ratios of leukocytes and the rates of sedimentation are wholesome *unless otherwise altered*. An excess of parasitic or of non-parasitic antigens in the internal environment effects almost immediate alterations in numbers and ratios of leukocytes and accelerates sedimentation. Recognition of these anomalies, if slight, may be difficult, but they usually are unmistakable and with other information are diagnostic and prognostic. This proof of the deficits in antibodies, likely the storage thereof, indicates the nature of aid to be given (*e. g.*, immune sera, ordinary and immunotransfusions of unmodified blood, glucose, etc.) if any be needed to protect or to hasten rehabilitation of the blood-forming and distributing structures.)

Summary. Formation and distribution of the constituents of blood and lymph are the fundamental functions of the living wherein every cell of a body participates.

Hemology; *i. e.*, hemo-lympho-cytology, hemo-lympho-plasmology and knowledge of the activities providing circulation and storage of the constituents of blood and lymph is consequently the basis of medical effort.

Qualitative and quantitative fluctuations in the constituents of blood and lymph, fluctuations in the total and unit volumes, in velocities, destination, storage and withdrawals from storage and utilization of proportions of blood and lymph are concurrent with changing living conditions.

Restrictions of fluctuations within wholesome limits maintains balances which are requisite to health.

Early recognition and interpretation of untoward alterations in constituents or in their distribution and storage reveal approaching or incipient disease (imbalance) indicate the antigenic or non-antigenic provocative influences and the most propitious preventive or corrective measures.

Repetition of examinations will establish the efficacy or inefficacy of measures *while they are being employed* by disclosing a reduction or an increment in untoward alterations and thus revealing progress toward or away from restoration and conservation of favorable balance upon which enduring recovery depends.

Additional knowledge is required to recognize lesser untoward alterations and wider experience to interpret them with dependable accuracy.

An appreciation of normal and morbid physiology that supplements hemology is requisite to progressive medical education and practice and to the investigations conducted in clinic and laboratory that will provide additional information imperatively needed.

HEMOLYTIC ANEMIA IN CARCINOMATOSIS OF THE BONE MARROW.

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It is a well recognized fact that profound changes often take place in the blood of persons suffering from malignant tumors. Far too frequently these are dismissed quite readily by the clinician on the basis of cachexia, without any effort being made to arrive at a satisfactory explanation. Such an attitude is as deplorable as the

once frequent use of the term "secondary" to designate all anemias which were not of the Addison-Biermer type. While there are exceptions, it is undoubtedly true that in the vast majority of cases of malignancy, one is able by careful study to arrive at a quite logical and satisfactory explanation of the hematopoietic disturbance.

If an attempt is made to analyze the causes of alteration in the morphologic blood picture in individuals with malignant growths (and by this we refer especially to cancer), one can find a very natural division into what might be called primary and secondary causes. Primary causes play a rôle when the abnormality of hematopoietic activity is brought about directly through the cancer cells themselves or chemical substances arising from them, that is their metabolic or excretory products. On the other hand, among the secondary causes we group those disturbances which result from the effect which the tumor growth exerts on other parts of the body and hence indirectly on the blood forming organs.

Before going on to a discussion of the changes in the blood due to the primary causes, it might be well to take up those resulting from secondary causes, as these are much more common and the mechanism of production for the most part is more obvious. These explain many of the changes which are frequently attributed to cachexia.

In a great many cases examination of the blood reveals a typically posthemorrhagic anemia. This is particularly the case in tumors of the stomach, large bowel, rectum and uterus. Persistent hemorrhages may occur from growths in these locations. Many times this loss of blood is not recognized until a very grave anemia results. Frequently in cases of carcinoma of the stomach with their accompanying achlorhydria, superficial examination of the blood has led to a diagnosis of pernicious anemia. This is in the vast majority of cases not a true pernicious anemia, but simply the result of a persistent blood loss, and careful examination shows that the blood findings lack all of the pathognomonic features of Addison's anemia. The cells are small with low hemoglobin concentration and if nucleated reds are present they are of the normoblastic or macroblastic type, in contrast to the megaloblastic forms of pernicious anemia. Moreover, there is not the reduction of myeloid white blood cells nor the thrombocytopenia and bilirubinemia of pernicious anemia.

Very rarely there do occur, however, cases of carcinoma of the stomach with the characteristic blood findings of pernicious anemia. We have one such in our records in which after a typical and rapid improvement in the anemia following liver therapy, the diagnosis of malignancy was confirmed by operation and histologic examination of the stomach. Whether these cases are to be interpreted as extraordinary combinations of the two conditions or whether the carcinoma plays a rôle in the production of the pernicious anemia,

is at present uncertain. In the light of our present knowledge it seems quite reasonable to presume that extensive malignancy in this organ might so disturb its functional activity as to lead to the particular changes necessary for the production of this specific form of anemia. On the other hand, it is extraordinary that the complication does not occur much oftener than careful analysis of the blood reveals.

In contrast to these cases showing posthemorrhagic anemias which really explain many of the anemias associated with cancer, we not infrequently encounter cases showing an increase in the number of red blood cells over the normal. These result for the most part from two main causes. First, in cases where, as for instance, in carcinoma of the esophagus the fluid intake is reduced and an anhydremia results, due to its quantitative reduction. In these cases we have a type of pseudopolycythemia and they may be readily recognized by the very high refraction index of the blood plasma. A second cause for increase in the red blood cells is anoxemia resulting from tumors of the thorax which interfere with the proper aëration of the blood. In these a true polycythemia, though of symptomatic type, results and figures well over 6,000,000 red cells per c.mm. may occur.

Turning more particularly to the changes in the white cells of the blood, it is very frequent in malignant tumors to find a leukocytosis. Differential examination shows as a rule an increase in myeloid cells, particularly the neutrophils and monocytes. The neutrophil forms often show more or less immaturity, that is a shift to the left, and frequently a comparatively large number of myelocytes. The eosinophils may or may not be increased and very often the lymphocytes are reduced. Many of these changes in the white cells are readily explained on the basis of inflammatory reactions which often accompany the tumor growth; while in those cases in which the blood loss has occurred the leukocytosis very likely, in part at least, is due to associated leukopoietic activity of the bone marrow.

Eosinophilia seems more particularly to occur in cases of lung involvement and may bear some relation to the associated bronchiectasis. The platelets of the blood are quite frequently numerous and it is rare, except in the more extraordinary pictures resulting from primary causes which we shall discuss later, to find any thrombocytopenia.

A hemorrhagic diathesis, however, may result from secondary causes in cases of obstruction to the bile ducts with jaundice and here it is interesting to note that the severity of the hemorrhagic condition seems to stand in more intimate relation to the length of time which jaundice has existed than to its severity. This suggests that it is not so much the jaundice as associated dysfunction of the liver parenchyma which lies at the basis of the prolonged bleeding.

In many cases of malignant growths the color of the blood plasma is not changed and there is no marked bilirubinemia. However, where obstruction to the bile channels, as mentioned above, occurs, a high bilirubinemia results with the typical van den Bergh findings of obstructive jaundice. Chemical examination of the plasma, in rapidly spreading growths, shows relatively early an increase in globulin and a decrease in the albumin proteins. This wou d appear to be one of the principal causes of the rapid sedimentation velocity and quite likely results from the destruction of tissue which occurs.

Returning now to the primary causes of changes in the blood in malignant tumors, we are treading for the most part on theoretical ground. Under this category we have to include changes which are directly referable to the presence of the cancer cells themselves in the hematopoietic organs, or changes which they effect in the blood cells through metabolic or chemical products liberated by them. Many of these anemic conditions in cancer are dismissed rather cursorily on the basis of "cachetic" changes; but if one attempts to analyze them more carefully, it is found comparatively difficult to derive from this phrase any satisfying explanation. The question naturally arises first, whether "malignant" cells more particularly cancer cells, phagocytose the red blood cells in sufficient numbers to produce an anemic state. In our experience this seems very doubtful. It is not uncommon to find iron pigment in cancerous tissue, but on the other hand many times it is absent and its presence seems to depend upon and be in direct proportion to the amount of hemorrhagic extravasation of blood in the tissues. Pigment is liberated in these extravasated areas, but it is doubtful if any appreciable phagocytosis of the erythrocytes by the cancer cells occurs.

It has been recognized for some time that in certain, though not all, cases of extensive metastases of cancer in the bone marrow, profound changes may take place in the blood. These consist of the presence of a large number of nucleated red cells, even though the anemia may not be severe. In addition myelocytes and even myeloblasts may be thrown into the circulation. In fact, these changes have been looked upon by hematologists for some time as suggestive, in certain cases, of metastatic carcinoma of bone. They generally have been explained on the basis of irritative effects on the myeloid tissue caused by the presence of the neoplastic cells. The fact that some cases of very extensive and diffuse metastases in the bone marrow may run their course without these blood changes has led to the general belief that the influence exerted by the cancer cells is not a mechanical disturbance, but rather due to "toxic" effects exerted by the cells upon the neighboring proliferating myeloid tissue. Why this effect should take place in some cases and not in others has not been explained. Moreover, it has been observed, particularly in cases of metastatic carcinoma of

bone with anemia, that the anemia was of hyperchromic type with high color index. By this we do not mean that the blood picture was in any way diagnostic of pernicious anemia, but rather that a macrocytic anemia with a preservation of high hemoglobin concentration was found.

Another change which has occasionally been reported in cases of generalized carcinomatosis is the presence of a considerable amount of hemosiderosis in the liver and spleen. This has been explained on the basis of "toxic" effects from the cancer cells leading to hemolysis of the erythrocytes in the vicinity, the pigment then being borne by the blood stream and stored in the reticulocyte of the spleen and liver. While such a theory is inviting, it is rather difficult to substantiate it.

It is quite obvious, therefore, from this review of our knowledge of blood changes in carcinoma, that those arising from secondary causes seem well established and their explanation is fundamentally sound, but that the changes attributed to primary causes remain indefinite and are covered by that common cloak of ignorance, the term "toxin," which is itself unsatisfactory in the final analysis.

It seems, therefore, worthwhile to record detailed and complete blood studies on two of these cases which seem to enable us to form a somewhat clearer conception of the basis and mechanism of the effect of some of these primary causes. These findings would seem to correlate and bring together into a more reasonable explanation some of these blood disturbances.

Case Reports. CASE 1.—The case which first brought this to our attention was that of a traffice officer, aged 58, who entered the hospital September 25 complaining of loss of weight, loss of appetite and general rundown condition for the past 6 months, aching pains in the legs for 6 months, impaired vision, diplopia, vomiting after meals, ringing in the ears and impaired hearing on the right side for 4 months.

The patient had enjoyed exceptionally fine health until the onset of the present illness 6 months previous to admission. At that time he had what he believed to be an attack of grippe with development of pain in both legs. Since then he had never felt well. About 2 weeks after the onset he lost his appetite and his weight dropped from 225 to 153 pounds. His vision gradually failed and recently his family noticed a prominence of his left eye and swelling about it.

Physical examination showed temperature and respirations normal, with pulse 94. His general appearance was that of a very emaciated man of stated age, slightly lethargic but intelligent and coöperative. His skin and mucous membranes were very pale. There was a definite swelling in the left temporal region causing protrusion of the left eye. The liver was palpable 4 cm. below the costal margin and a small hard mass could be felt to the right and above the umbilicus. The spleen was not palpable. The inguinal glands were hard and immovable and considerably enlarged. Rectal examination showed the prostate to be fixed and very hard with obliteration of the median furrow and induration extending into the adjacent structures.

Laboratory examination showed the urine to be acid with a faint trace of albumin and specific gravity 1.012. The Wassermann reaction was

negative. Roentgen ray examination of the lumbar vertebræ, pelvis, ribs and scapulæ showed sclerosing bone changes suggestive of secondary carcinoma. There was no evidence of metastases in the lungs. The body of the twelfth dorsal was collapsed. The skull was negative.

Morphologic Blood Examination. Red blood cells, 1,900,000; white blood cells, 3000; hemoglobin, 35% (5.46 gm. per 100 cc.); color index, 0.92; red blood cells stain well. Marked anisocytosis and poikilocytosis. Moderate polychromatophilia. No punctate basophilia or nucleated reds. Reticulated reds, 6%; fragility, markedly increased; corpuscle volume, 16%; averaged corpuscle volume, 84 cu. μ; Hemoglobin concentration, 0.97; sedimentation velocity, very rapid.

White blood cells (400 examined):

	%	Per c.mm.
Neutrophils	61.25	1837
Eosinophils	2.0	60
Mast cells	0.25	8
Monocytes	4.5	135
Lymphocytes	32.0	960

Reduction in all forms, particularly myeloid elements.

Platelets, 86,000; irregular in size and shape.

Bleeding time normal. Coagulation: fibrin, 3 min.; congealing, 6 min.; with calcium, 6 min.; retraction present.

Plasma, pale yellow with greenish tinge. Refraction, 49.

Van den Bergh: Direct: prompt, negative; delayed, positive; indirect: 2 units bilirubin.

Microscopic Fragility Test:

	Unhemolized +000	%
Tube 100	1500	100.0
70	1020	68.0
65	800	53.0
60	540	36.0
55	140	9.3
50	40	2.7
45	0	0.0
40	0	0.0
35	0	0.0
30	0	0.0

The morphologic blood picture shows striking changes which point distinctly to a severe hemolytic type of anemia with interference with bone marrow activity. The hemolytic character of the anemic condition is shown by the number of reticulated red cells, the markedly increased fragility of the erythrocytes, the bilirubinemia with a delayed, positive, direct van den Bergh reaction and the preservation of a high hemoglobin concentration.

The general myelophthisic character of the blood picture is indicated by the marked reduction in myeloid white cells, the thrombocytopenia and the lack of nucleated reds.

It seems fairly certain, therefore, that this blood picture is the result of a combination of two factors: (1) a hemolytic process and (2) a general interference with myeloid activity.

Unfortunately this patient was discharged from the hospital immediately following the blood examination and before the results had been received and the extraordinary character of the case realized. Efforts to bring about a readmission were unsuccessful, and even more disappointing was the fact that we were unable to obtain an autopsy at the time of his death, approximately 3 months later.

Although no biopsy was performed, there seemed little doubt the patient was suffering from a primary carcinoma of the prostate with extensive metastases in the osseous system.

At this time we did not realize the possible significance of the severe hemolytic type of anemia and were inclined to attribute the combination of extensive carcinomatosis and this form of anemia to an extraordinary coincidence.

Somewhat later, however, a second case came to our attention which, in a great many respects, was similar to the first, and this impressed upon us the fact that we were dealing in both cases not with a coincident but rather with an associated and extraordinary form of reaction on the part of the hematopoietic system in generalized carcinoma of bone. Fortunately in the second case we were able to carry out a thorough clinical examination followed by autopsy findings.

CASE 2.—This case was that of a housewife, aged 49, who entered the Royal Victoria Hospital June 10, complaining of pain in the back and legs, weakness, dyspnea and palpitation. One year previous she had had the right breast removed at another hospital. The pathologist reported a rapidly growing carcinoma situated immediately beneath the nipple, without evidence of invasion of the deeper tissues or axillary glands. She remained in good health to within 3 months of the present admission, when the pain and weakness first appeared.

Physical examination showed a sallow color with slight cyanosis, no glandular enlargement or palpable masses, a purpuric rash over the chest, abdomen and lower back, the spleen enlarged down to the umbilicus and very firm, and the liver just palpable. Temperature, 100° F.: pulse, 110; respirations, 25.

Laboratory examinations showed the urine to be free of Bence-Jones protein, free acid of gastric contents 10° and total acid 20°, stools dark in color with no occult blood, and the Wassermann reaction negative. Roentgen ray of the osseous system failed to show any rarefaction of the bones, but dark shadows were present in the lungs, suggestive of metastases.

Morphologic Blood Examination. Red blood cells, 2,300,000; white blood cells, 8300; hemoglobin, 41% (6.4 gm. per 100 cc.); color index, 0.9; red blood cells: cells on average small, but stain well. Few macrocytes. Marked anisocytosis, slight poikilocytosis and polychromatophilia. No punctate basophilia. Twenty-two nucleated reds in 300 white blood cells, as follows: 3 orthochromatic and 13 polychromatic normoblasts; 3 polychromatic and 3 basochromatic macroblasts. Corpuscle volume, 18%. Average corpuscle volume, 78 cu. μ. Hemoglobin concentration, 1; reticulated reds, 8%; fragility, markedly increased.

White Blood Cells (300 examined):

	%	Per c.mm.
Neutrophils	44.6	3702
Metamyelocytes	4.0	332
Oxy. myelocytes	12.6	1046
Neutrophilic myelocytes	6.6	548
Eosinophils	2.0	166
Mast cells	1.6	133
Monocytes	8.3	689
Lymphocytes	20.3	1684

Many immature and perverted myeloid forms.

Platelets: 26,000; scarce, but normal size and shape. Bleeding time moderately prolonged. Coagulation: fibrin time, rapid; congealing time,

prolonged (20 minutes); calcium time, prolonged; retraction slow but marked.

Plasma, dark yellow with marked greenish tinge. Van den Bergh: direct: prompt, negative; delayed: strongly positive; indirect: strongly positive, 6 units bilirubin.

The blood picture is that of a hemolytic anemia with other extraordinary features.

The erythrocytes show an increased fragility with a considerable number of reticulocytes. They tend to preserve a good hemoglobin concentration, as is the rule in hemolytic conditions. In addition there is a considerable number of nucleated red cells in various stages of development. Some of these are macroblastic forms.

The leukocytosis is only slight, but there is a distinct tendency for immature and perverted myeloid forms to enter the circulation. The reduction in platelets is marked and with this goes the prolonged bleeding time and alteration of the coagulation time met with in other thrombocytopenic conditions. The bilirubinemia completes the picture.

Here again the blood picture is: (1) a profound hemolytic anemia and (2) myelophthisic changes with thrombocytopenia and hemorrhagic diathesis.

The patient rapidly declined and died on June 30. Autopsy showed extensive metastasis of the breast carcinoma in the lungs, liver, bone marrow and cervical and mediastinal lymph nodes.

The neoplastic areas in the bone marrow were extraordinary in that they consisted for the most part of emboli of tumor cells, definitely within vascular channels. These cells had apparently proliferated there, dilating and distorting the walls, but only occasionally was there evidence of actual spread and growth among the myeloid elements. This did occur, however, with the formation of accompanying fibrous stroma. The result of this high degree of vascular embolization was a profound circulatory disturbance, without appreciable actual displacement of functioning bone marrow elements by the neoplastic cells. Extensive hemorrhagic extravasations had occurred about the tumor plugs into the myeloid tissue, and in these disintegration of erythrocytes was obviously taking place.

No positive evidence of phagocytosis of the red blood cells or their cell detritus by the cancer cells could, however, be demonstrated. In some areas the extravasation of blood into the marrow reached a mild degree of infarction. There was no granular pigment, and stains for iron were negative. In areas where the myeloid tissue was best preserved it was found to be actively erythropoietic with numerous erythroblasts in various stages of development. It was also very hemorrhagic.

The spleen weighed 780 gm., was firm and the cut surface hemorrhagic. Histologic sections showed a large amount of blood in the pulp, considerable myeloid metaplasia and many large phagocytic cells containing granules of pigment, which gave a positive reaction for iron (hemosiderin). The parenchymal cells of the liver also showed a large amount of similar pigment. No pigment, however, was present in large cancer areas elsewhere in the body.

Discussion. There seems no reason to doubt but what in this second case we are again dealing with a hemolytic anemia in generalized carcinomatosis. It is, of course, possible that both these cases represent simple coincidents. However, it is difficult to explain them on this ground, and it seems much more reasonable to believe that the diffuse carcinomatosis involving the marrow is a distinct etiologic factor in the production of the hemolytic condition.

The histologic studies carried out on the bone marrow show extensive plugging of the larger vascular channels by the cancer cells which has led to the formation of extensive hemorrhagic extravasations. In some of these areas the extravasated blood remains free, while in others there is distinct evidence that it has undergone coagulation with the formation of fibrin and fusion and disintegration of the red cells. It is a well established fact that such extravasated blood undergoes hemolysis with the formation and deposition of hemosiderin, which might be taken by some as a satisfactory explanation of the hemolytic anemia. To our minds, however, such an explanation is not satisfactory. In the first place, it does not explain the increased fragility of the circulating erythrocytes nor does it explain the changes in the spleen, such as the engorgement by blood of the pulp with compression of the venous sinuses—a picture quite characteristic of hemolytic jaundice.

We are, therefore, rather of the opinion that there may occur in the body, as a result of extensive carcinomatosis of bone, a generalized alteration in hematopoietic activity, which is of such a nature as to lead to the changes necessary for the production of a typical hemolytic anemia. Moreover, it is possible that the explanation of this phenomenon may lie in extensive embolization of the vascular channels of the myeloid tissue by tumor plugs with consequent profound circulatory disturbances and hemorrhagic extravasations.

Whether the alteration in the fragility of the erythrocytes to hypotonic salt solution, which was present in both cases, is of primary importance in the pathogenesis of the anemia or only a secondary phenomenon, is difficult to decide. Unfortunately studies were not carried out on the diameters of the red blood cells, so we are unable to state whether the shift to a smaller but thicker, *i. e.*, spherical, type of erythrocyte occurs here, as we have been able to demonstrate in other forms of anemia with increased fragility. However, it seems to us a very interesting point, if our conclusions are correct, that we have in these cases an example of a hemolytic anemia in which the primary etiologic factor is apparently definitely known, although the mechanism of production still remains in doubt.

Moreover, as regards the incidence of metastases in the bones, there is no question but what a great many cases of tumor-spread, in which even Roentgen ray examination may fail to show evidence of metastases, nevertheless eventually disclose extensive involvement of the osseous system. The frequency of metastatic involvement of bones by malignant tumors is much higher than is generally supposed, as was recently shown by Schmorl. By careful examination, both grossly and histologically, of the vertebral column, he was able to demonstrate the presence of metastases in 66% of all cancers of the prostate, 33% of primary cancers of the bronchi, 33% of bladder cancers and 40.7% of all sarcomata. Moreover, in similar examinations carried out on 500 autopsies of cases of malignant tumors of

various parts of the body, he was able to demonstrate vertebral metastases in 19.6% of the men and 15% of the women. These figures are most interesting, and certainly show the incidence of metastases in the bones to be much higher than has been previously believed. Undoubtedly many cases have gone unrecognized, where thorough studies of the bones were not carried out.

Summary. Therefore, two facts confront us: first, that by a thorough and detailed examination of the blood we are able to demonstrate in certain cases of "malignant" growths a hemolytic form of anemia, which in the presence of more superficial examination would likely be passed over as merely secondary or explained on the basis of cachexia; and second, that a more detailed and systematic examination of the bones in cases of these tumors reveals an extraordinarily high percentage of metastases in the osseous system.

In the light of this evidence, therefore, we cannot but feel that a more thorough study in the directions indicated would possibly establish this phenomenon as not too uncommon a cause of the severe anemias in the presence of "malignant" growths. It seems, therefore, advisable to continue these investigations, and it is for the purpose of inviting these that this fragmentary report is offered.

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BACTERIOPHAGE SERVICE TO PATIENTS WITH STAPHYLOCOCCUS SEPTICEMIA.*

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Scope. In 1932 we presented a report[1] on the bacteriophage treatment of 15 patients with staphylococcus bacteremia. Since that time a few additional cases have been presented in the papers from our laboratory but there has been no published analysis of a series of consecutive observations. Now we have records of 163 patients with staphylococcus septicemia for whom we have rendered bacteriophage service. We have chosen, however, to limit the present discussion to the 100 consecutive cases immediately following in time the 15 reported in 1932, namely Patients 16 to 115. Some of the more general features will be presented in this present paper and the more intimate study of the 100 patients will follow in the next paper.

Consideration of the nature of bacteriophages, their sources, technique of propagation, titration, testing and packaging for clinical use will be omitted from this paper. We purpose here to consider the practical application of these lytic agents in the treatment of septicemia. This in itself is a research problem worthy of careful study.

Diagnosis. The diagnosis of staphylococcus infection and bacteremia requires some discussion. For our purpose, and for practical clinical work also, in our opinion, only the positive blood culture or evidence of metastatic localization of staphylococcus infection can be accepted as adequate proof of staphylococcus bacteremia and of these the blood culture occupies first position. The blood culture should be made in such a way as to yield the most convincing evidence. We ordinarily draw the blood from the elbow vein into citrated saline solution in a Taylor[2] tube, avoiding any contact with the outside air. Coagulation is prevented by mixing the blood with the citrate. Measured portions are then added to melted agar to produce a smooth mixture of agar and blood and plated before the medium becomes solid. Measured portions of the citrated blood

* These studies have been aided by a grant from the Josiah Macy, Jr., Foundation.

are also transferred to bottles of broth, some of which may be covered with sterile oil if desired, although this is unnecessary for growth of the staphylococcus. After the agar is solid all the cultures are placed at 37° C. Growth of the staphylococcus can often be recognized within 24 hours, nearly always after 2 days and very exceptionally the colonies may be first found on the fourth day. A count of the colonies affords an approximate measure of the number of viable bacteria per cc. of blood and comparison of the plates and broth cultures affords evidence of the reliability of the entire procedure. The positive blood culture is the point of departure for preparation of the specific bacteriophage for the patient and under no circumstances should these plates and bottles be prematurely destroyed.

Staphylococcus infection which has not yet invaded the blood stream may be recognized sometimes by experienced observers on the basis of clinical evidence, as for example in a furuncle, but, in general, a bacteriologic examination of exudate from the local lesion is necessary for accurate diagnosis. The early specific etiologic diagnosis of such local lesions may permit the proper early treatment to forestall a bacteremia. Once the infection of the blood stream has become established the local lesion becomes subordinate in importance, a fact sometimes not fully appreciated by the less experienced surgeon. At the moment we are not especially concerned in dicussing such local lesions, although local application of bacteriophage may be helpful.

Therapeutic Technique for Septicemia. After the diagnosis of staphylococcus bacteremia has been established we have recommended the immediate use of our stock bacteriophage and at the same time the prompt preparation of a specific phage. This specific phage is prepared by subjecting a culture of the organism from the patient's blood to lysis by a mixture of stock phages. The filtrate of this lyzed culture contains a potent bacteriophage adapted to the specific organism as well as specific bacterial proteins. The preparation of this specific phage, including adequate sterility tests, may require 2 to 8 days. During this interval of waiting, the stock phage is employed in therapy.

When there are recognizable local lesions we apply copious amounts of broth phage to the open surfaces and inject through a fine needle (gauge 27) the asparagin phage into the lymph spaces all about the lesion. These injections are repeated every 24 to 48 hours and the local applications are made at each dressing. Chief reliance, however, is placed upon the intravenous injections of the asparagin bacteriophage. Once the bacteremia is recognized we prefer to postpone operative procedures and transfusions for at least 24 hours and during this time, the intravenous bacteriophage

injections are pushed to produce a shock reaction. Evidence of serious cardiac or pulmonary disease is reason for greater caution but even here we try to cause a "reaction."

The injections are made through a fine needle (gauge 27) and great care is exercised to avoid permanent injury to the vein. Ordinarily one makes the entire series of injections into the same site without extravasation or thrombosis. We like the flat tourniquet[3] of garter elastic, as it permits accurate adjustment of pressure, easy release by one hand and is less annoying to the patient than a cylindrical tourniquet. We prefer, when possible, to keep away from the elbow veins, reserving these for transfusions and avoiding any responsibility for their destruction by the phage injections. Veins on the hands, forearms, feet, ankles and neck may be used to advantage. To preserve the vein one removes the tourniquet before beginning the injection and applies pressure over the puncture in the vein *immediately* upon withdrawing the needle, maintaining an adequate even pressure here for a full five minutes. This is best done by applying the tourniquet to hold the compression pad. Leaving this after-care of the vein to an uninstructed nurse often results in extravasation of blood. Elevation of the part and rest from movement are helpful. While we shall not cite specific examples, there are in our series instances in which intravenous therapy was discontinued because of technical difficulty in keeping the veins in good condition during the many injections required.

We begin with a small intravenous dose, ordinarily 0.5 cc. but sometimes with as much as 2 cc. if the colony count in the blood is above 50 per cc. The doses are spaced at approximately 45 minutes and are increased in arithmetic progression 0.5–1–2–3–4–5–6–7–8–9–10 cc. and then continued as 10 cc. doses until about 100 cc. total amount has been administered. Then one increases to 15–20–25 or even 30 cc. at one injection. If a shock occurs at any time during the series the injections are discontinued for 8 to 20 hours or until the next morning. If shock does not occur the prognosis is not so good. Therefore we like to persist, but it is probably wise to stop at a total of 100 cc. in children under 5 years, 200 cc. in those under 15 years and 300 cc. in older persons, even if no reaction appears. In such cases one makes a renewed attempt to shock the patient on the third or fourth day or as soon as a specific phage is ready. Rectal temperature is recorded every hour while the series of injections is being given.

When there is reason for greater haste the doses may be increased more rapidly in series, as for example, 1–2–4–8–12–16–20–25–30 cc. This saves the doctor's time but is probably more dangerous for the patient with enfeebled circulation or pulmonary involvement.

The shock reaction may be forecast by a slight rise in temperature. Often, however, it begins without warning by complaint of feeling cold, pallor and cyanosis of extremities and of face, chattering of the teeth and general and highly distressing rigor. We ordinarily apply external heat, administer oxygen by nasal catheter, give adrenalin and rarely morphin. Having warned the patient in advance that we expect to produce a chill we now attempt to reassure him and the anxious family by expressions of satisfaction that the chill has come. Serious immediate danger appears to be confined to patients with soft endocardial vegetations which may be dislodged during this reaction. After shaking for 5 to 70 minutes the temperature is ordinarily between 104 and 107° F. Then the patient suddenly ceases to shake. He becomes rosy and breaks out in profuse perspiration. The temperature falls rapidly in an hour and by the next morning may be below 99 or even below 98. After the chill ceases the patient ordinarily feels at peace with the world and usually goes to sleep and remains quiet for several hours.

On the day when such a series of doses is given the patient should not be subjected to transfusion nor to surgical incision, because these may confuse the clinical picture. Saline solution may be given intravenously if desired.

For 2 or 3 days after the shock reaction the patient is given smaller doses, morning and evening. Ordinarily the dose employed is approximately $\frac{1}{2}$ the last dose of the series which was followed by the shock reaction. For example if, on the first day, the patient had received at intervals doses of 1–2–3–4 cc. and then developed a chill, we give on the following day an intravenous dose of 2 cc. in the morning and again in the evening and continue the same doses for 2 or 3 days. On these days transfusion may be given and easily accessible purulent collections may be drained. If the blood culture remains positive another attempt to shock the patient is undertaken on the fourth day and again on the seventh day. When the blood culture becomes negative we continue the small intravenous doses twice daily for a week or two, then once daily for about a month. When the patient is allowed to be out of bed we change to subcutaneous injections, 2 or 3 times a week, continuing these for 3 to 6 months. The treatment is varied to meet the particular situation and greatest attention is given to the results of blood cultures taken once or twice each week.

Temperature, pulse rate, blood pressure and body weight are carefully recorded and frequent physical examination is not neglected. The urine is examined frequently. Infarction of the kidneys is very common in staphylococcus bacteremia. In most instances these renal lesions heal with continued intravenous bacteriophage therapy.

A further consideration of the various complications and metastatic localizations of the infection will be omitted.

Examples of Success and Failure. Somewhat detailed records of patients who survived and of others who died have been presented in our earlier publications. Each patient presents an individual problem and it seems worth while to include here as examples the records of 2 patients of the present series, 1 who survived and 1 who succumbed.

CASE 1.—A. W. (*Patient No. 59*), male, aged 39, was admitted to the Post-Graduate Hospital on July 12, 1933 (Fig. 1). He had fallen ill 2 days before, with vague abdominal distress, weakness and fever. A blood culture taken at that time was positive and we identified *S. aureus*. Another blood culture taken after admission to the hospital (July 14) yielded the same organism and a third blood culture taken on July 16 was similar. Urine culture taken on July 17 remained negative. Bacteriophage therapy was requested on July 18 by the physician, Dr. A. W. Duryee, to whom we are indebted for the clinical record, and the bacteriophage treatment was given by us personally. On July 18 after taking a blood culture, an intravenous injection of 0.5 cc. stock asparagin staphylococcus bacteriophage was given in 2 minutes at 12.20 P.M. This was followed an hour later by 1 cc. intravenously. At 2.50 P.M. the patient had a slight chill; external heat was applied and his temperature rose to 100° F. At the time this did not seem to be a definite reaction to bacteriophage but, because the clinical condition of the patient seemed satisfactory, no more phage was given on that day. On subsequent days an intravenous dose of 0.5 cc. bacteriophage was given twice daily. On Saturday, July 22, an attempt was made to push the bacteriophage injections to a shock reaction. Signs of left pleurisy had been recognized on the previous day and the specific bacteriophage was ready for use. On July 22, a preliminary blood culture was taken at 8.50 A.M., and then at 9.04 A.M. an intravenous injection of 0.5 cc. of the specific phage was given. This was followed by 1 cc. at 9.47 A.M.; 2 cc. at 10.32 A.M.; 4 cc. at 11.22 A.M.; 8 cc. at 12.20 P.M.; 10 cc. at 1.25 P.M.; 10 cc. at 2.18 P.M.; 10 cc. at 3.19 P.M.; 12 cc. at 4.05 P.M. and 12 cc. at 4.50 P.M. The total amount for the day was 69.5 cc. The patient remained comfortable, without chill or any evident reaction although his temperature reached 102.4° at 6 P.M. At the time we were seriously disappointed at this failure to induce a shock but later, when it became evident that the infection of the blood stream had already disappeared, the failure to produce a shock seemed to be explained. Subsequently smaller doses of the specific phage were continued until the patient was discharged on August 9. The pleurisy and the infiltration of the left lung had entirely disappeared by this time and the patient left the hospital in good condition.

After discharge from the hospital, the patient continued to receive subcutaneous injections of bacteriophage once or twice a week. Apparently this treatment was discontinued some time in October or November. Early in December he developed a furuncle on the side of his neck and this was treated by us on December 10 and 12, with prompt relief. At this time the patient was urged to continue with the subcutaneous injections at the hands of his physician in order to forestall further activity of the infection. After a few weeks this was again discontinued.

On April 15, 1934, the patient was again admitted to the hospital with fever and tenderness over the right kidney. Cultures of the blood and of the urine were negative. Because of the previous history it seemed probable

that we had to deal with a septic infarct of the kidney. However, in the absence of more certain criteria, it was decided to explore the right kidney. Preceding the operation an intravenous injection of 2 cc. of his specific bacteriophage was given at 1.33 P.M. and the operation, begun at 3.36 and completed at 4.10 P.M., disclosed an abscess of the lower pole of the right

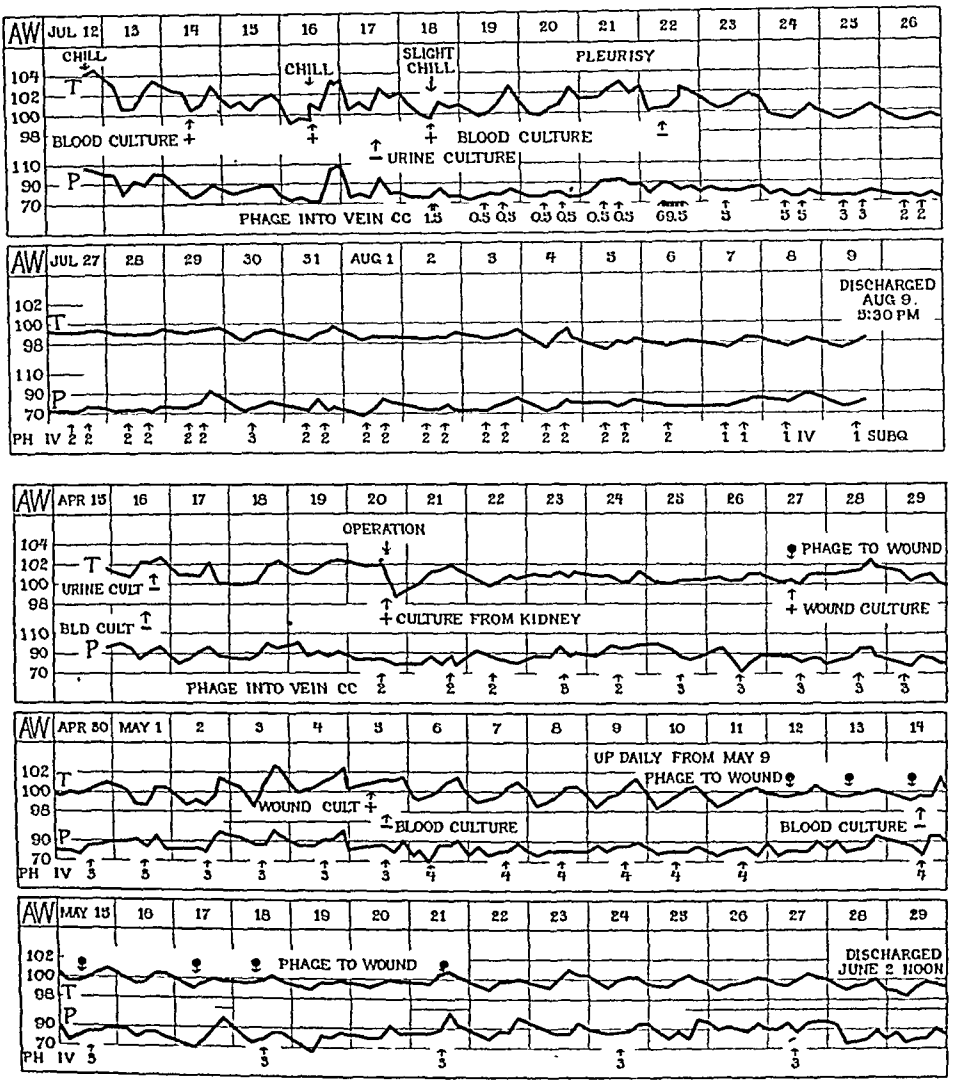


FIG. 1.—Abridged clinical record of A. W., male, aged 39, during two admissions to the hospital, namely July 12, 1933, to August 9, 1933, and April 15, 1934, to June 2, 1934.

kidney with a perinephritis. This was incised and drained. Cultures of the exudate gave a growth of *S. aureus*. The postoperative course was rather uneventful. Intravenous bacteriophage was given daily until May 11 and at intervals of 3 days thereafter until discharge from hospital on June 2. Subcutaneous injections of bacteriophage twice a week were continued thereafter for some months. The patient has remained well.

The record of this patient serves to illustrate some features of the bacteriophage therapy of staphylococcus sepsis which are now fairly well established. When the treatment is begun before there are destructive lesions in the vital organs, the outlook is better. If the infection of the blood stream is such that only a few colonies of staphylococcus develop in the blood culture, then the intravenous injection of a relatively small amount of bacteriophage will usually be sufficient to cause a chill. In this particular case the colonies were always less than 1 per cc. of blood and the blood culture taken on July 18, just before starting the bacteriophage injections, gave positive growth of *S. aureus* in only one broth flask and none on the plates. The patient chilled after only 2 intravenous doses, 0.5 and 1 cc., of bacteriophage. Subsequently, on July 22, when we again attempted to cause a chill reaction, the patient failed to react although a series of 10 injections, from 9.04 A.M. (0.5 cc.) to 4.50 P.M. (12 cc.) amounting to a total of 69.5 cc. bacteriophage, were given intravenously within 8 hours. On this date the blood culture taken just before the first injection of bacteriophage remained sterile. This result is in accord with our conception gained from other similar experiences, namely, that the typical shock reaction comes when the amount of bacteriophage injected has the proper quantitative relation to the bacteria in the blood stream. If the blood stream is sterile one may fail to produce a reaction even with large amounts of bacteriophage. Also when the blood stream is heavily infected or when massive collections of bacteria are directly in relation to the blood, as in vegetative endocarditis, one may have to administer very large amounts of bacteriophage before the patient reacts. We believe that the shock reaction is not due directly to substances contained in the bacteriophage itself but that it is brought about by an interaction, probably opsonic, between the bacteriophage and the accessible bacteria.

This record also illustrates the very common tendency for staphylococcus bacteremia to result in renal infarction. In our experiments on rabbits, kidney infarction has been very common and in our series of human septicemias it has been rather frequent. In the patients, the renal infection often heals without incision when adequate intravenous bacteriophage treatment is given.

The record of this patient also illustrates the danger of metastatic localization of the infection as a sequel to the bacteremia. It is true that not all patients fall victims to such later manifestations, but these late lesions have been common enough in our series for us always to recommend continuation of bacteriophage injections for a period of 3 months after apparent complete recovery from a blood stream infection with staphylococcus.

CASE 2.—As an example of unfortunate result we have chosen Y. R. (*Patient No. 90*), female, aged 6, under the care of Dr. W. D. Crecca of Newark, New Jersey, to whom we are indebted for the case record. She fell ill on Sunday, February 18, with a chill and general discomfort. On February 19 the left ankle was painful and the temperature ranged from 101° to 104°. Upon admission to the hospital on February 22 the temperature was 100°, pulse 120; a soft systolic blow was heard at the apex of the heart. There was swelling with fluctuation over the medial malleolus of left ankle. On February 22 at 11.38 A.M. pus was evacuated from the lower end of the left tibia and a plaster dressing applied. Blood culture taken on February 23 gave a growth recognized as *S. aureus* on February 24 and on this day bacteriophage was obtained from us by messenger. Beginning at 7 P.M. intravenous doses were given at intervals, 1–1–2–3–4–5–6–7 cc. stopping at 1 A.M., February 25. There was no evident reaction. About 8 A.M. February 25, the dressing was removed and 20 cc. bacteriophage was applied to the wound, and at 10 A.M. 4 cc. phage was given intravenously. The condition appeared very grave and Dr. Crecca asked us to see the patient and continue the bacteriotherapy. At 6.40 P.M. we took a blood culture and then began a new series of intravenous phage doses, 5 cc. at 6.45 P.M. ending with 22 cc. at 1 A.M., the total amount being 114 cc. There

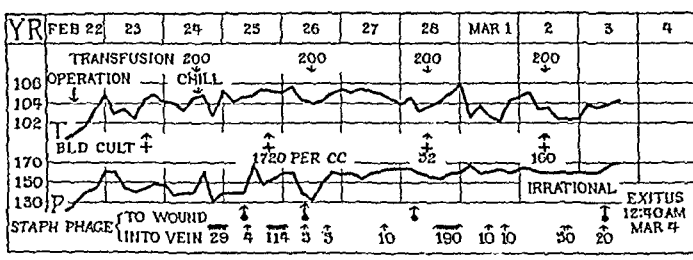


FIG. 2.—Abridged clinical record of Y. R., female, aged 6, during her treatment in hospital, February 22 to March 4, 1934.

was no reaction and the situation appeared hopeless. On the next day the rich growth in the blood culture was evident and the colony count after 48 hours' incubation of this blood culture taken on February 25 amounted to 1720 per cc. of blood. Smaller doses of phage were continued on February 26 and 27 and on February 28, because the patient was still alive and somewhat brighter, we were again called to Newark. The blood culture taken on February 28 yielded only 52 colonies per cc. In the afternoon and evening a total of 190 cc. of bacteriophage was given intravenously in divided doses between 3 P.M. and 11 P.M. without definite reaction, although there was perhaps a suggestion of reaction in the temperature rise to 106° at midnight and fall to 102.8° at 4 A.M. March 1. On March 1 we were somewhat encouraged by the lower colony count on the blood culture of February 28 and by the lower temperature of the patient. The pulse rate, however, remained high. Bacteriophage, 10 cc., was given twice on March 1. On this day extensive consolidation of the left lung was recognized and there was also evidence of meningeal irritation, but the cyanosis was less. On March 2 a blood culture was taken at 10 A.M. and a transfusion given. This blood culture later developed 160 colonies per cc. of blood. Bacteriophage was discontinued. In the evening, however, at the earnest insistence of the parents we were again called to continue the bacteriotherapy. At this time the pneumonia was very extensive, respirations 76 per minute, the patient was irrational with moderate rigidity of extremities and neck.

After 2 intravenous injections of 25 cc. each the injections were stopped. On March 3, however, another intravenous dose of 20 cc. phage was given at 10 A.M. and the wound was irrigated with phage. Death occurred at 12.40 A.M., March 4, with extensive pneumonia and terminal meningitis. Autopsy was not permitted so that the condition of the heart remains uncertain.

The record of this patient resembles that of several other children in our series, who were subjected to operation for osteomyelitis. When the infection of the blood stream is already established these children do not seem to withstand very well a bone operation under general anesthesia. On that account we now favor a more conservative program of intravenous bacteriophage therapy to overcome the septicemia before attacking the local lesion in the bone. However, each patient presents a special problem and judgment is difficult. Children with rheumatic or congenital defects of the heart are particularly handicapped in the fight against an infection of the blood stream even without the added burden of an anesthetic and surgical shock. The importance of the preliminary blood culture is evident.

At the present time we should not be satisfied to stop after a total dose of 29 cc. of intravenous bacteriophage in such a case. One should keep on trying to induce the shock reaction until the total dose has reached at least 100 cc., unless definite clinical contraindications become manifest.

The reduction in number of bacteria in the circulating blood from 1720 per cc. on February 25 to 52 per cc. on February 28 is noteworthy and it appears to have resulted from the bacteriophage treatment. We have not yet seen a recovery after the blood culture has revealed more than 250 colonies per cc. of blood. The observation in this case encourages one to believe that even such a high colony count may not be a certain indication of fatal outcome.

Summary. 1. The diagnosis of staphylococcus septicemia should be supported by positive blood culture made in such a way as to give reliable evidence of the approximate number of viable bacteria in the blood of the patient.

2. The technique of the bacteriophage therapy is described.

3. The shock reaction to intravenous bacteriophage appears to depend upon interaction between the bacteria, the bacteriophage and the natural defense mechanisms of the host.

4. An example of success and an example of failure are presented.

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ONE HUNDRED PATIENTS WITH STAPHYLOCOCCUS SEPTICEMIA RECEIVING BACTERIOPHAGE SERVICE.*

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The selection of the 100 patients for the present list has been made on the basis of objective criteria. First, there must have been received by us a request for bacteriophage service and therefore the series may be regarded as unselected. Second, there had to be reasonably convincing evidence that a blood stream infection with staphylococcus actually existed. In most instances there were repeated positive blood cultures and the organism was submitted to us for study. We have, however, included in the list several patients who died without a proper culture being submitted to us and a few patients have been included without acceptable evidence that a positive blood culture was ever obtained. When one considers that relatively few of these 100 patients were seen by us in person, it is noteworthy that decision as to admitting or excluding a patient from this list did not more frequently meet with serious difficulty. All patients who died have been included even if the evidence of staphylococcus sepsis seemed rather frail. We have stopped arbitrarily at Patient 115 in consecutive order, thus reserving for a later discussion the rapidly growing list of patients coming to our records after August 11, 1934. There were some patients whose records presented particular difficulty as will be evident in the later discussion.

Relation to Season of Year. Table 1 presents data of patients with staphylococcus bacteremia from No. 16 to No. 115 inclusive. At first glance one is struck by the fact that the period February 3 to August 8, 1932 has 12 recorded cases with no survivals. From August 9 to November 28, 1932, inclusive, there were, however, 5 recoveries in a series of 10 cases. This is followed by another period of discouraging experience from December 3, 1932 to June 2, 1933, inclusive, during which time 16 patients were given bacteriophage service for septicemia without any recoveries. Since June 3, 1933, every period of 2 months contains at least 1 successful case. Possibly this variation in mortality may have been related to the season of the year, to alterations in virulence of the disease or to a combination of fortuitous factors which are unrecognizable. During 1932

* These studies have been aided by a grant from the Josiah Macy, Jr., Foundation.

and 1933 more recoveries were observed in cases treated in the last half of the year as compared with the first half. In the first half year of 1932 we gave service to 10 patients without a recovery; in the corresponding portion of 1933 to 15 patients with 1 recovery and in the first half of 1934 to 23 patients with 5 recoveries, making a total of 42 deaths and 6 recoveries. On the other hand, for the period July 1 to December 31 in 1932, we served 15 patients with 5 recoveries; in 1933 in the second half 29 patients with 11 recoveries and in 1934 from July 1 to August 12 there were 8 patients with 3 recoveries, making totals of 33 deaths and 19 recoveries.

Other possibilities require consideration. We see in this record a challenge to close scrutiny of the technical methods employed in the preparation of the bacteriophage filtrates used in treatment and we are inclined to believe that these agents may have been more suitable at certain particular times. The stock bacteriophage has not been standardized and every effort is still being made to increase its efficacy in the light of continued experience.

TABLE 1.—DATA ON 100 CASES OF SEPTICEMIA RECEIVING BACTERIOPHAGE.

No.	Date.*	Patient.			Clinical conditions.	Operation.	Positive blood culture.	Death.
	1932							
16	Feb. 3	DC	M	21	Purulent arthritis of knee, septicemia	Feb. 5	Feb. 2	Feb. 15
17	Apr. 12	CW	M	36	Apr. 7, sepsis after hemorrhoidectomy	Mar. 28	Apr. 10	Aug. 8
18	May 3	JR	M	67	Apr. 19, gangrene left foot, diabetes	Apr. 26	Apr. 20	June 10
19	May 19	EH	M	35	May 17, furuncle of nose, extending	May 19	May 17	May 20
20	May 26	AZ	M	62	May 18, urinary infection	None	May 21	May 26
21	May 28	AC	M	61	May 7, furuncle on finger; May 21, chill	None	May	May 31
22	May 28	ML	F	48	May 24, severe chill of cryptic origin	None	May 26	May 29
23	May 30	FE	M	31	May 23, cryptogenic sepsis	None	May 30	May 31
24	June 8	KP	F	26	June 2, furuncle on face	June 6	June 6	June 11
25	June 22	FH	F	18	June 14, furuncle on arm; June 17, chill	None	June 20	June 23
26	July 26	EP	F	26	July 17, sepsis after childbirth, July 16	July 27	July 17	Aug. 4
27	July 31	EK	F	12	July 6, multiple furuncles; appendectomy	July 27	July 29	Aug. 17
28	Aug. 9	TO	M	25	July 7, nasal furuncle	July 14	July 21	Recovery
29	Aug. 9	LH	M	39	May 26, osteomyelitis of fibula	Many	Aug. 2	Sep. 9
30	Aug. 24	EH	F	15	Aug. 5, puncture wound of foot	Aug. 19	Aug. 21	Recovery
31	Sep. 23	LB	F	8	Sep. 18, pansinusitis; sepsis	Sep. 18	None	Oct. 5
32	Oct. 5	MU	M	21	Sep. 19, fracture of sternum; mediastinitis	Oct. 5	Oct. 6	Recovery
33	Oct. 17	BO	F	61	Oct. 1, sacral carbuncle; diabetes	None	Oct. 15	Oct. 19
34	Oct. 20	GT	F	47	Oct. 10, carbuncle; diabetes	Oct. 10	Oct. 14	Nov. 5
35	Nov. 10	HL	M	15	Oct. 7, osteomyelitis of femur	Oct. 16	Oct. 11	Recovery
36	Nov. 17	PS	M	16	Nov. 2, contusion of thorax; osteomyelitis	Nov. 16	Nov. 16	Nov. 17
37	Nov. 28	DM	F	11	Nov. 19, furuncle of face	None	Nov. 25	Recovery
38	Dec. 3	JB	F	47	Oct. 21, furuncle of nose; sepsis	Many	Oct. 28	Dec. 16
39	Dec. 22	LC	M	15	Dec. 13, osteomyelitis; epidural abscess	Dec. 14	Dec. 20	Jan. 1
40	Dec. 24	MI	F	12	Dec. 14, cryptogenic sepsis, tachycardia	None	Dec. 21	Dec. 28
	1933							
41	Jan. 20	MM	F	17	Jan. 17, extraction of tooth	Jan. 17	Jan. 18	Jan. 21
42	Jan. 20	MH	F	17	Dec. 23, osteomyelitis of ilium	Dec. 28	Jan. 19	May 12
43	Jan. 24	FS	M	35	Dec. 22, fracture of skull base	Jan. 12	Jan. 5	Jan. 29
44	Jan. 24	VM	F	21	Dec. 31, cryptogenic fever	Jan. 23	Jan. 21	Jan. 24
45	Jan. 26	EC	F	11	Empyema; myocardial abscesses	Jan. 24	Jan. 24	Jan. 26
46	Feb. 9	MT	F	4	Feb. 2, osteomyelitis of foot	Feb. 6	Feb. 5	Feb. 9
47	Feb. 10	SR	M	71	Jan. 14, furuncles on back of neck	Feb. 7	Feb. 9	Feb. 15
48	Feb. 18	CO	F	16	Jan. 25, acute mastoiditis	Jan. 28	Feb. 3	Mar. 13
49	Apr. 4	GS	F	25	Mar. 26, abortion; sepsis	None	Apr. 2	Apr. 8
50	Apr. 4	JP	M	32	Feb. 28, furunculosis; pyemia	May 2	None	May 27

* This is the date when our bacteriophage service was requested in each respective case.

No.	Date.*	Patient.			Clinical conditions.	Operation.	Positive blood culture.	Death.
	1933							
51	May 3	AR	M	27	Old osteomyelitis; operation Apr. 28	Apr. 28	Apr. 29	May 4
52	May 20	NT	F	45	May 1, compound Colles' fracture	May 1	May 20	May 25
53	May 27	EK	M	57	May 18, carbuncle on forehead	None	May 27	May 29
54	June 3	HP	M	21	Apr. 22; sore throat and malaise	May 21	May 11	Recovery
55	June 17	SK	F	31	June 12, pustule on chin	None	June 16	June 17
56	July 1	AR	F	49	June 29, renal abscess	Many	June 29	Recovery
57	July 10	AN	M	57	June 9, abscess of left knee; osteitis	Yes	July 8	Oct. 8
58	July 15	HK	M	19	June 25, carbuncle on neck	June 25	July 11	July 16
59	July 18	AW	M	39	July 10, cryptogenic fever	None	July 12	Recovery
60	Aug. 3	JM	M	11	July 12, polyarthritis; heart murmur	None	July 21	Aug. 25
61	Aug. 7	HP	M	13	July 31, baseball injury to thigh	None	Aug. 4	Aug. 19
62	Aug. 21	LB	M	36	Leukemia and terminal sepsis	None	Aug. 19	Aug. 26
63	Aug. 26	GK	M	36	Aug. 2, infected finger; pyemia	Aug. 22	Aug. 24	Aug. 28
64	Aug. 31	HC	M	41	Aug. 25, meningitis; endocarditis	None	Aug. 28	Aug. 31
65	Sep. 2	DM	M	23	Aug. 5, carbuncle on forearm; pneumonia	None	Aug. 31	Recovery
66	Sep. 3	MC	F	8	Aug. 28, cellulitis of face	None	Aug. 29	Recovery
67	Sep. 13	LM	M	33	Sep. 5, osteomyelitis for 20 years	Sep. 11	Sep. 13	Sep. 16
68	Sep. 15	MP	F	25	Aug. 12, childbirth; Aug. 14, chill	None	Aug. 17	Recovery
69	Sep. 23	AM	M	37	Sep. 14, furuncle of nasal septum	None	Sep. 20	Sep. 23
70	Sep. 26	SG	M	21	Aug. 14, furunculosis	None	Sep. 14	Oct. 5
71	Oct. 10	TH	M	29	Sep. 21, compound fracture of ankle	Oct. 4	Oct. 6	Recovery
72	Oct. 28	LW	F	19	Oct. 16, purulent arthritis of hip	Oct. 26	Oct. 26	Oct. 31
73	Nov. 3	RS	F	31	Nov. 1, severe headache and fever	None	Nov. 1	Nov. 3
74	Nov. 13	FD	M	16	Nov. 10, fever of cryptic origin	Nov. 11	Nov. 10	Recovery
75	Nov. 14	CW	M	0	Ill since birth on Oct. 21	None	Nov. 11	Nov. 16
76	Nov. 14	RL	F	3	Oct. 23, pneumonia	None	Nov. 1	Recovery
77	Nov. 17	RW	M	5	Nov. 8, osteomyelitis of leg	Nov. 15	Nov. 15	Recovery
78	Nov. 25	FD	M	27	Nov. 9, cryptic fever with cough; empyema	None	Nov. 20	Recovery
79	Nov. 29	JK	M	8	Nov. 21, cryptic fever; appendectomy	Nov. 23	Nov. 27	Recovery
80	Nov. 30	RM	M	31	Nov. 22, furuncle of nose	None	Nov. 29	Dec. 1
81	Dec. 6	RJ	M	53	[illegible]	None	Sep. 10	June 4
82	Dec. 10	AK	M	40	[illegible]	Nov. 1	Dec. 8	Dec. 12
83	Dec. 22	AE	F	6	[illegible]	Nov. 17	Nov. 14	Dec. 31
84	Dec. 25	CT	F	14	Dec. 23; chills, fever; endocarditis	None	Dec. 25	Dec. 26
	1934							
85	Jan. 9	EO	F	24	Dec. 30, furuncle on face	Jan. 7	Jan. 6	Jan. 18
86	Jan. 24	VC	F	12	Jan. 16, fever blister on lip	None	Jan. 22	Jan. 26
87	Jan. 26	VH	F	12	Jan. 7, osteomyelitis of heel	Several	Jan. 15	June 20
88	Jan. 27	CB	M	64	Jan. 1, cryptogenic septicemia	None	Jan. 17	Recovery
89	Feb. 21	EM	M	28	Jan. 16, recurrent old osteomyelitis	Feb. 1	Feb. 17	Recovery
90	Feb. 24	YR	F	6	Feb. 18, cryptic fever; osteomyelitis	Feb. 22	Feb. 23	Mar. 4
91	Mar. 12	WL	M	66	Feb. 25, angina, cervical adenitis	Mar. 6	None	Mar. 14
92	Mar. 18	GB	F	38	Dec. 25, furunculosis, empyema	Mar. 5	Mar. 16	Mar. 22
93	Mar. 20	WJ	M	46	Mar. 1, nephrectomy; Mar. 22, thoracotomy	Mar. 1	Mar. 19	Mar. 23
94	Mar. 31	NG	F	44	Mar. 26, cryptogenic fever	None	Mar. 28	Apr. 1
95	Apr. 22	JB	M	26	Apr. 13, carbuncle of nose	Apr. 17	Apr. 19	Recovery
96	Apr. 24	GS	M	65	Apr. 18, furunculosis, stupor	Apr. 14	Apr. 18	Apr. 24
97	May 1	MW	M	40	Mar. 25, furuncle on neck, septicemia	None	Apr. 28	May 5
98	May 8	AJ	F	80	May 2, furuncle on face, diabetes	May 8	May 6	May 9
99	May 10	EB	F	15	Mar. 20, furuncle on face, pyemia	July 7	May 7	Recovery
100	May 13	MD	F	12	Mar. 26, otitis media; mastoidectomy	Apr. 13	May 10	Recovery
101	May 24	MT	F	10	May 7, furuncle on back; osteomyelitis	May 21	May 21	June 8
102	June 6	LS	M	34	Wound of thumb on Dec. 24	Dec. 24	Jan. 19	June 15
103	June 7	GB	M	0	May 25, a feeble infant; otitis media	None	June 4	June 8
104	June 11	AC	M	20	June 7, fulminating otitis media	June 5	June 10	June 13
105	June 20	CB	M	16	June 14, osteomyelitis after thumb wound	June 15	June 18	June 22
106	June 23	HM	M	19	Apr. 30, diabetes and sepsis	May 9	May 7	July 3
107	June 27	DD	F	10	June 24, osteomyelitis, endocarditis	June 24	June 24	July 24
108	July 3	KH	M	37	May 4, wound of thumb; sepsis	Yes	June 20	Recovery
109	July 6	DC	M	11	June 21, abdominal pain	None	June 30	July 14
110	July 18	WN	M	16	July 14, tooth extraction; sepsis	July 14	July 17	Recovery
111	July 28	SG	M	39	July 25, infected varicose veins	July 26	July 25	Aug. 2
112	July 30	EO	F	31	June 26, childbirth; June 28, chill	July 16	July 23	Recovery
113	Aug. 6	RM	M	15	Aug. 2, pain in thigh; osteomyelitis	Aug. 18	Aug. 4	Aug. 23
114	Aug. 11	TC	F	4	Aug. 4, cellulitis of foot	Aug. 8		Aug. 13
115	Aug. 12	NS	M	62	July 7, cystotomy; Aug. 7, prostatectomy	Aug. 7	Aug. 11	Aug. 15

* This is the date when our bacteriophage service was requested in each respective case.

Relation to Other Factors. Of far greater significance, however, are factors which do not appear at once in such a chronologic table. Among these may be mentioned age and sex of the patient, condition of the vital organs, such as heart, lungs, brain, kidneys, at the start of bacteriophage treatment, susceptibility of the infecting organism to bacteriophage lysis, virulence of the infection, delay in instituting treatment and wisdom exercised in carrying out the treatment.

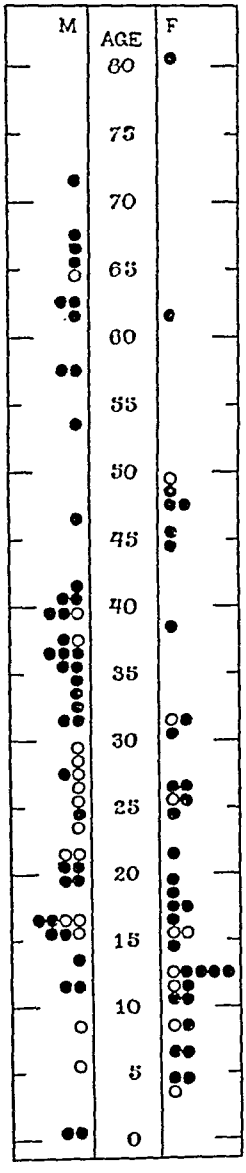


FIG. 1.—Distribution according to age and sex of 100 cases of staphylococcus septicemia. Hollow circles indicate survivals and solid black circles indicate deaths.

As to distribution according to sex and age (Fig. 1), there were 42 females and 58 males, an apparently insignificant difference. One boy was 15 days old and another 3 months old; 1 woman was 80 years old. Evidently no age is exempt from this disease. In the first decade of life there were 4 boys with 2 survivals and 7 girls with 2 survivals. In the second decade there were 12 boys with 3 survivals and 17 girls with 4 survivals. One therefore sees a suggestion that females under 20 years are more frequently afflicted than are the males of the first two decades of life. From ages 20 to 39, inclusive, however, the males greatly predominated in this series and that in spite of the occurrence of staphylococcus puerperal sepsis in the females. In the third decade there were 12 males with 8 survivals and 6 females with 1 survival, and in the fourth decade 15 males with 2 survivals and 4 females with 1 survival. Beyond age 40 there were 15 males, the oldest 71 years of age, and of these only 1, a man of 64 years, survived; while there were only 8 females over 40 with 1, aged 49, surviving. One gets the impression, which will require confirmation by larger figures, that patients under 30 years have a better prognosis and that the males between 15 and 30 years constitute the group with best chance for survival.

Susceptibility of the Staphylococcus to the Available Bacteriophages. In most instances the staphylococcus of sufficient virulence to invade the blood stream is found to be susceptible to lysis by our stock staphylococcus bacteriophage. There are, however, a few exceptions in this series. Somewhat resistant bacterial strains were encountered in Patients 62, 78, 81 and 106. Patient 62 was dying

of leukemia complicated by sepsis, and serial filtrations to enhance the lytic action of the phage were discontinued upon death of the patient. In the other 3 cases we succeeded in enhancing the lytic power to full potency by repeated filtration of cultures in series. In 2 instances, Patients 82 and 89, the culture submitted to us was found to be completely resistant to our stock bacteriophage and attempts to enhance the lytic activity were discontinued because further bacteriophage therapy was not desired. In 20 cases of the series we failed to receive a culture of the infecting organism in spite of repeated requests. In 74 cases the culture from the patient was found completely susceptible to our stock staphylococcus bacteriophage in the first trial. In general we have the impression that the staphylococcus resistant to bacteriophage is of relatively lower virulence than the phage-susceptible strains, but further observations are required before an unreserved statement can be made in regard to this point.

The Survivals. The surviving patients require particular consideration. There are 25 ranging in age from 3 years to 64 years.

Survivals. The youngest patient to recover, R. L., *No. 76,* a female, aged 3, was admitted to the Perth Amboy General Hospital on October 23, 1933, with diagnosis of pneumonia, second degree burn of the right chest wall and excoriation of buttocks. Blood cultures taken on November 1 and November 11 yielded *S. albus.* A total amount of 8 cc. of stock staphylococcus bacteriophage was given intravenously on November 14 and the injections were continued subsequently in small doses. On January 17, 1934, Dr. H. P. Fine reported a complete recovery.

A boy of 5, R. W., *No. 77,* was admitted to the Methodist Episcopal Hospital, Brooklyn, on November 12, 1933, with osteomyelitis of the leg which began with pain on November 8. The knee joint was opened on November 15 and pus evacuated. Blood culture taken on November 15 and again on November 17 yielded *S. aureus.* Stock staphylococcus bacteriophage was requested and used locally and intravenously from November 17 to November 21. On that day the specific preparation was ready and its daily use begun. After drainage of an abscess of the thigh on November 21 bacteriophage therapy was discontinued. Blood cultures were negative on November 23, 28, December 10 and 13. The femur was opened on December 6, and on January 5, 1934 the limb was sacrificed by thigh amputation. The patient was discharged March 11 and the wound was entirely healed on June 10, 1934.

M. C., *No. 66,* a girl of 8, was admitted to the Essex County (New Jersey) Hospital August 28, 1933, with furuncle and cellulitis of the face. Blood culture of August 29 gave a heavy growth of *S. aureus.* Blood cultures of August 31, September 2 and 4 were positive. On September 3, intravenous doses of stock staphylococcus bacteriophage to a total of 19 cc. were given, probably a series of 1–2–3–5–8 cc., followed by the usual shock reaction with temperature rise to 105.6. On September 6 another series of doses to a total amount of 23.5 cc. was followed by a similar reaction with temperature rise to 104. Subsequently smaller doses of bacteriophage were given and the patient received repeated transfusions. She was discharged October 7; evidently too soon, for she was admitted to the Orange Memorial Hospital with osteomyelitis on October 24 and was again treated with intravenous phage. She was discharged March 1, 1934, with persistent sinus and was reported as walking on June 4, 1934.

No. 79, J. R., a boy of 8, was admitted to Bellevue Hospital November 21, 1933, where an appendectomy was performed. Subsequently there was recognized osteomyelitis of the right femur, left tibia, left fibula, left humerus, and left radius as well as suppurative pleurisy. Blood culture of November 27 was positive for *S. aureus*. The record says with 1000 colonies per cc. Bacteriophage treatment was begun on November 29, 1933, and continued until about December 15. The patient remained in the hospital for a year under treatment for the localized areas of osteomyelitis. Many operations were performed for drainage. He was discharged, improved, on December 16, 1934.

No. 87, D. M., a girl of 11, was admitted on November 25, 1932, to the Jamaica (New York) Hospital with cellulitis of the face, which began about November 19. Blood culture taken on admission yielded *S. albus*. Temperature ranged between 102 and 104. Bacteriophage intravenously in divided doses to a total of 36 cc. was administered on November 29 without reaction. After an interval of 9½ hours this treatment was continued to a total amount of 12 cc. in this second series, whereupon there was a chill with cyanosis and rise in temperature to 103.4. On the next day the temperature dropped to 99.6, and did not go above 102 again during her stay in the hospital. There was no further bacteriophage therapy. The patient was discharged December 24, improved.

No. 100, M. D., a girl of 12, was admitted to the Greenpoint Hospital, Brooklyn, on March 26, 1934. On April 13 a simple mastoidectomy was performed. On April 22 the left wrist became painful. On May 12 a thrombosed jugular vein was ligated and opened. The blood culture of May 10 yielded staphylococci and on May 13 a blood culture yielded streptococci. These cultures were not made available for examination by us. Staphylococcus bacteriophage was given intravenously to a total amount of 28.5 cc. on May 13, without evident reaction. The patient recovered and was discharged on May 23, 1934. This case is included in our series with a great deal of reserve. We are inclined to question the validity of the first blood culture. It seems not improbable that this was an ordinary case of streptococcus mastoiditis with jugular thrombosis.

E. H., *No. 30*, a girl aged 15, was admitted to the Long Island College Hospital on August 18, 1932, with sepsis following punctured wound of a toe. The leg was incised on August 19. Blood culture taken August 21 yielded 54 colonies of *S. aureus* per cc. of blood. Stock staphylococcus bacteriophage was given intravenously in divided doses to a total amount of 29.5 cc. on August 24 and also was applied to the wound. Smaller intravenous injections were continued until September 11. Blood cultures on August 25, 29 and September 8 were negative. The patient was discharged on June 28, 1933, with persistent sinuses. On July 26, 1934, she was walking with crutches.

No. 35, H. L., a boy aged 15, was admitted to the Yonkers (New York) General Hospital October 7, 1932, for osteomyelitis of left femur, following an abscess on right elbow which was then healing. Blood culture taken October 11 yielded *S. aureus* and further positive blood cultures were obtained on October 14, 17, 24 and November 4. A staphylococcus vaccine was given subcutaneously on November 5 and 6. On November 11 an extensive operation was performed removing the necrotic cortex of middle third of the femur. Bacteriophage was applied locally at this time. On November 13 Savita* bacteriophage was given intravenously in 2 doses, 0.5 and 1 cc., followed by a chill with cyanosis and temperature rise to 104.8. On November 18 a total amount of 2.5 cc. was given intravenously

* Savita bacteriophage is bacteriophage prepared in a medium containing vegetable proteins supplied by Savita, a meat substitute. This medium was used only for a short period of time in our laboratory.

in 3 doses. On November 19, 6 doses, total amount 15.5 cc., were given intravenously. The patient complained of feeling cold and temperature rose to 104 and fell to 99 to remain down all the next day. Smaller doses were continued up to November 24 and on this day the newly prepared specific bacteriophage was given intravenously, a total of 9 cc. in 2 doses, after which there was a chill at 2 P.M. lasting 45 minutes and temperature rise to 106.6 with fall to 99 at midnight rising again to 101 on third day afterward. Phage was used locally only after this time. He was discharged January 19, 1933, in good condition.

E. B., *No. 99*, a girl of 15, was admitted to the Perth Amboy General Hospital on May 7, 1934, with cellulitis of the face and neck, lobar pneumonia of the upper left lung and embolic lesions in the skin. The admission note states that she was moribund. Blood culture was taken on May 7 and again on May 8 and the doctor has informed us that these cultures were positive for staphylococcus. Laboratory records are not available. Intravenous bacteriophage was started at 8.10 P. M. on May 10 and continued until 1.50 A.M. on May 11, the total amount being 36 cc. intravenously. There was no chill but there was free diaphoresis at 1.45 A.M., and at 4.15 A.M. the temperature had fallen to 101.4. The patient was distinctly better on this day. Smaller injections of bacteriophage were continued for at least 10 days during which time the cellulitis of the face and neck cleared up. Blood cultures were consistently negative after June 5. A metastatic abscess of the left hip was incised and drained on July 7. The lung cleared gradually and she was discharged September 25 in good condition.

No. 110, W. N., a boy aged 16, was admitted to the Alexian Brothers Hospital, Elizabeth, N. J., on July 16, 1934, suffering from sepsis following tooth extraction. Blood culture taken on July 17 gave a growth of *S. aureus* and on July 18 the bacteriophage was given intravenously in divided doses to a total amount of 15.5 cc. Following this there was a slight chill, and diaphoresis. On July 19 a series of 7 intravenous doses to the total amount of 65 cc. was followed by slight chill and sweating. After moderate doses for a few days he was given a total of 85 cc. on July 24 without evident reaction and on July 25 a total amount of 45 cc., after which there was a severe shock and a temperature rise to 107. Small intravenous injections were continued daily during the patient's stay in the hospital. He was sent home from the hospital on August 29 and was able to be up and about during December, 1934. Patient was reported to be doing well on January 15, 1935.

F. D., *No. 74*, a boy aged 16, was admitted to the Mary Immaculate Hospital, Jamaica, N. Y., on November 10, 1933, with a diagnosis of acute osteomyelitis. Blood culture taken November 10 was reported positive on November 13 for hemolytic *S. aureus*. On that account bacteriophage was requested and was furnished by us on November 13, 1933. When this material arrived at the hospital it was decided that the blood culture could not be regarded as positive and therefore the bacteriophage was not used. The boy was discharged from the hospital on November 19. On December 1, 1933 he was readmitted to the hospital and discharged again on December 12, to be readmitted on January 10, 1934, and discharged on January 14. At the time of the third admission there were multiple abscesses in different parts of the body and the doctor informs us that on the basis of the clinical evidence there must have been a blood stream infection. Culture taken from one of these abscesses in January, 1934, yielded *S. aureus*. Autogenous vaccine was given to the patient and his condition was reported as entirely satisfactory on January 14, 1935. This patient is included in our series with considerable reserve but we decided not to exclude him because he appears to have made a recovery from a decidedly questionable bacteremia without the use of bacteriophage. In this series we have included

all patients in whom there is definite reliable evidence of a septicemia with staphylococcus in the blood stream for whom we have been asked to furnish bacteriophage. Whether the bacteriophage was used or not has not been a criterion for including or excluding the patient. As will be seen later this is the only patient in the entire series who recovered without the use of bacteriophage. The others for whom the bacteriophage was not used, succumbed.

No. 52, M. U., a man aged 21, was admitted to the Students Health Service, University of Minnesota, September 23, 1932, following a fracture of the sternum in football practice on September 19. Bacteriophage was requested by telegram on October 5, 1932, and forwarded by air mail. This was given intravenously on October 7 to a total amount of 5 cc. Subsequently a broth bacteriophage was applied to the mediastinal wound. The patient has been reported by McKinley and his associates.[1] He recovered and was able to play football again in November, 1934.

No. 54, H. P., a man, aged 21, was taken ill on April 24, 1933, with sore throat followed by pneumonia. Blood culture taken on May 11 gave a growth of *S. aureus* and there were several subsequent positive blood cultures. Bacteriophage was given first on June 5 and specific autogenous phage was used first on July 10. The patient made a complete recovery. This case has been reported in detail by Dr. W. M. Gilbert.[2]

No. 65, D. M., a man, aged 23, was admitted to the Grasslands Hospital, Valhalla, N. Y., on August 5, 1933, with a carbuncle on right forearm. Subsequently pneumonia and septicemia developed. Blood culture taken on August 31, 1933, yielded 170 colonies of *S. aureus* per cc. of blood. Blood cultures taken on September 1 and September 9 were also positive. Stock staphylococcus bacteriophage was requested and given September 2, 1933, at which time we received a culture from the blood. The bacteriophage was used intravenously from September 2 to September 8. At that time the specific preparation was available and its use begun and continued until October 26. A blood culture taken September 28 remained negative and the patient was discharged as recovered on December 3, 1933. He was admitted again on January 23, 1934, with myocardial insufficiency and ascites. Again he received intravenous bacteriophage from February 14 to February 28 and the ascitic fluid was evacuated. He was discharged February 28. On July 28, 1934, he reported again for treatment of a furuncle. At this time his general condition was good.

No. 68, M. P., female, aged 25, was delivered of her third child at the Greenpoint Hospital, Brooklyn, on August 12, 1934, without laceration. On August 14 she had a chill and temperature rise to 104. Blood cultures taken on August 17, 19 and 28 gave growth of staphylococcus. Those taken on September 15 and September 29 remained sterile. On August 23 a right parametrial pelvic thrombophlebitis was recognized and later a septic nephritis and septic pneumonia. The bacteriophage was given intravenously on September 17, at first in a dose of 0.5 cc., and was gradually increased to 2 cc. morning and afternoon. The patient left the hospital on October 2 and follow-up indicates satisfactory and complete recovery.

No. 28, T. O., male, aged 25, had an abscess of the nasal septum beginning with pain on July 7, 1932; incised on July 14. Patient was admitted to the Long Island College Hospital on July 14. Blood culture taken on July 21 gave positive growth of *S. aureus* and it was positive on several occasions thereafter but only a few colonies appeared at any time. Blood cultures taken on August 8 and 15 remained sterile. Metastatic pneumonia, septic nephritis and pyemic abscesses in various parts of the body were observed and the staphylococcus was found in abundance in all these situations. A bacterial vaccine was injected subcutaneously on August 6, 7 and 8. Bacteriophage was given intravenously on August 9 without any attempt

to produce a shock and daily therafter in doses of 1 cc. until September 13, when the patient was allowed out of bed. He was discharged on September 20 and in December he was entirely recovered and "none the worse from his long and difficult experience."

No. 95, J. B., male, aged 26, had a papule on the right side of nasal septum on April 13, 1934. This extended and was incised on April 17. He was admitted to the West Hudson Hospital, Kearny, N. J., on April 19 and blood culture taken on that day gave a growth of *S. aureus*. Subsequent blood cultures were negative. Bacteriophage was given intravenously on April 22, a dose of 0.5 cc. at 1 A.M.; 1 cc. at 1.40 A. M.; 2 cc. at 2.20 A.M.; 3 cc. at 3 A.M.; 4 cc. at 3.40 A.M.; 5 cc. at 4.20 A.M.; 10 cc. at 5 A.M.; 10 cc. at 5.40 A.M.; 10 cc. at 6.20 A.M.; 10 cc. at 7 A.M. and 10 cc. at 7.40 A.M.; a total of 65.5 cc. in about 7 hours. The patient's temperature remained at 101.6 to 101.8 during this time and was 101.6 at 8 A.M., but rose rapidly to 105 at 10.30 A.M., descending again to 100.6 at 8 P.M. At 9.15 P.M. an intravenous injection of 5 cc. phage was given and at midnight the temperature reached 106, the highest point, descending to 100.6 at 6 A.M., April 23. Beginning at 10 A.M. on April 23, intravenous phage was given every 45 minutes to 7 P.M., a total amount of 75.5 cc. The highest temperature was 102 at 8 P.M. A precisely similar course of treatment was given on April 24 and on this day the highest temperature was 100.4. After that the temperature did not again exceed 99 and the patient was discharged from the hospital on April 29 and on May 7 the face was finally healed without scar.

No. 78, F. D., male, aged 27, developed fever, chills and productive cough about November 4, 1933, and was admitted to Morrisania Hospital on November 9 with physical signs of pulmonary exudate in both lower lobes. The temperature reached 105.4 on November 11 and 106.6 on November 14 and 15. Blood culture taken on November 20 yielded *S. aureus* and fluid from the right pleural cavity on December 19 revealed the same organism. Bacteriophage was given intravenously on November 25 in gradually increasing doses at intervals beginning with 1 cc. at 1.30 P.M. and ending with 7 cc. at 6.40 P.M., the total being 30 cc. This was followed by a chill and temperature rise to 106 at 7.30 P.M. and prompt fall to 99.8 at 8 P.M. Intravenous bacteriophage was continued in smaller doses until December 29, after which time the temperature remained below 99. Blood culture taken on November 30 yielded one colony of staphylococcus and subsequent ones were negative. Thoracotomy was not performed. Roentgenograms revealed a persistent thickened pleura. The patient was discharged as cured on January 6, 1934.

No. 89, E. M., male, aged 28, had osteomyelitis of lower third of right femur for about 20 years. About January 16, 1934, this region became painful and on February 1 he entered St. Peters Hospital, Brooklyn, where an abscess on the lateral aspect of the femur was incised. The pus contained *S. aureus*. The patient developed a septic temperature and blood cultures taken on February 17 and February 19 gave growth of the same organism. On February 22 at 10.25 A.M. 0.5 cc. of bacteriophage was given intravenously and continued in gradually increasing doses at intervals of 30 to 50 minutes until 7 P.M., when a total amount of 75.5 cc. had been given. There was no shock but some increase in sweating at 11 A.M. The temperature rose gradually from 97.8 at 10.25 A.M. to 104 at 8.30 P.M. Morphin sulphate gr. $\frac{1}{4}$ at 2.40 P.M., gr. $\frac{1}{6}$ at 5.30 P.M. and gr. $\frac{1}{6}$ at 7 P.M. may have played a part in suppressing the reaction but this is merely a surmise. On February 25 amputation was done at lower third of right thigh after which the temperature became normal and the amputation wound was healed completely on April 28, when the patient was discharged. The attending surgeon believed that the bacteriophage was without beneficial

effect and the removal of the focus of infection by amputation on February 25 resulted in the change in course of the disease.

No. 71, T. H., male, aged 29, suffered a compound fracture of the right ankle on September 21, 1933. Subsequently he developed septicemia and multiple metastatic abscesses. The blood culture was repeatedly positive with *S. aureus* and *Strep. hemolyticus*, single or mixed together. After a desperate and prolonged illness, during which transfusions, staphylococcus bacteriophage and streptococcus serum were employed, the patient recovered and was discharged from hospital on March 23, 1934. This case has been made the subject of a separate report.[3]

No. 112, E. O., female, aged 31, multipara, was delivered at the Community Hospital, New York City, of a stillborn child on June 26, 1934. Sepsis developed on June 28. Repeated transfusions were given and an abscess in the right broad ligament was drained on July 16. A positive blood culture was obtained on July 23, reported first as hemolytic streptococcus and later recognized as *S. aureus*. The temperature reached 107 on July 21, 23, 24, 27, 29 and August 5, and on July 19 and August 4 it reached 108. The highest temperature observed was 108.6 on July 25, at which time the patient was in a convulsion. Bloody sputum from abscess in the right lung and purulent urine showed abundant staphylococci mixed with an apparently anaërobic bacillus which failed to grow in culture. Blood cultures remained negative except for the one taken on July 23. On July 30, streptococcus serum was given and after further study of the blood culture, staphylococcus bacteriophage was given intravenously in divided doses to a total of 7 cc. This was followed by a chill and temperature rise to 106.4 with drop to 99.2 the next morning. Intravenous bacteriophage was continued in smaller doses daily until August 29 and thereafter in subcutaneous doses until September 28. The patient was discharged November 4 and was reported in perfect health in March, 1935. This case will probably be reported elsewhere in detail by Dr. H. P. MacGregor and his associates.

No. 108, K. H., male, aged 37, injured his left thumb with a piece of steel on May 4, 1934 and was admitted to St. Johns Hospital, Long Island City, on May 18 with osteomyelitis of the thumb from which *S. aureus* was isolated. Blood culture taken on June 20 and another on June 21 gave growth of the same organism. An abscess of the left foot was noted on July 1. Intravenous bacteriophage was given first on July 3, a total of 75.5 cc. in divided doses from 4.50 A.M. to 5.30 P.M. and again on July 6, a total of 75.5 cc. from 11 A.M. to 9.30 P.M. Following this second course the temperature rose to 103 and fell to 99.2 the next morning. On July 10 he received 55.5 cc. followed by a sharp temperature rise to 105 at 6.15 P.M. and a fall to 97 at 4 A.M. following. Another series of injections to a total of 21.5 cc. were given on July 11 and another series on July 13 to a total of 75.5 cc. Apparently the recommended small daily doses of phage were omitted but we are uncertain as to this because the record available to us is not very detailed. Positive blood culture was obtained on September 4 and September 20 and blood culture taken on September 28 remained negative. The patient was discharged in good condition on November 25.

No. 59, A. W., male, aged 39, suddenly became ill on July 10, 1933. He was admitted to the Post-Graduate Hospital on July 12, 1933, and finally discharged on June 2, 1934. His abridged clinical record has been presented in the preceding paper.[4]

No. 56, A. R., female, aged 49, had received treatment for a right ureteral calculus in the Beth El Hospital, Brooklyn, from June 2 to 19, 1933. After ureteral instrumentation the concretion was expelled on June 13. After antiseptic treatment she was discharged on June 19. At home she had an irregular fever, at times as high as 104 and was again admitted to the same

hospital on June 23, with pyelonephritis. Left pleurisy with effusion was recognized on June 25 and pneumonia in both lower lobes was found on June 27. The patient's temperature reached 105 on June 28 after a chill. A blood culture taken June 29 yielded 30 colonies of *S. aureus* per cc. of blood. Intravenous injections of phage were begun at 5.20 P.M. on July 1 and continued at intervals of 40 to 60 minutes until 12.10 midnight, the total amount being 58.5 cc. Twenty minutes later, at 12.30 A.M., July 2, there was a chill lasting 20 minutes and the temperature reached 106.4, falling quickly to 103 at 4 A.M., 101 at 8 A.M. and 99.6 at 4 P.M. on July 2. An intravenous dose of 5 cc. phage was given at noon on July 2 and then doses of 2 cc. were given morning and afternoon, apparently with considerable irregularity, until August 31. Blood culture taken on July 3 yielded 2 colonies of staphylococcus per cc. and one taken on July 8 showed a "few" colonies. Five more blood cultures taken during her stay in the hospital remained negative. Multiple pyemic abscesses appeared and these were treated conservatively. Some resolved without drainage, others healed after aspiration of the pus and some were incised and irrigated with phage. She was discharged on December 29. We are informed that she developed more abscesses after leaving the hospital but was much improved in June, 1934.

No. 88, C. B., male, aged 64, a private patient of Dr. Russell Cecil, developed fever and intestinal stasis about January 1, 1934. A preliminary diagnosis of intestinal neoplasm could not be confirmed by roentgenologic study. About the middle of January a positive blood culture was obtained and a few days later several teeth were extracted. He was seen by us in consultation on January 27, and, after taking a blood culture, which later yielded 218 colonies of *S. aureus*, stock bacteriophage was given intravenously at intervals of about 40 minutes beginning with 1 cc. at 2 P.M. and ending with 26.5 cc. at 6.45 P.M., the total amount being 100 cc. Small intravenous doses were given on the next 2 days. On January 30 at 7.55 A.M. a blood culture was taken which later developed only 12.5 colonies per cc. of blood and then the newly prepared specific phage was given intravenously in 10 cc. doses morning and evening. On February 1 this phage was given in a series of injections to a total of 90 cc. after which there was a chill. Another series of injections, total amount 150 cc., was given on February 8 and this series was followed by a moderate shock reaction. Bacteriophage treatment was then discontinued, contrary to our advice. Blood culture taken on February 11 yielded 42 colonies per cc. of blood. The patient was clinically improved at this time. Subsequently pyuria was recognized with staphylococcus in the urine. Apparently this resulted from a renal infarct. He continued to improve, spent a comfortable summer, after which he returned to his professional work, apparently normal.

Of these 25 patients only 3 were seen by any of us in person. To the others we furnished bacteriophage and suggestions for its use upon request of the attending physicians and our information concerning the clinical features and also the cultures transmitted to us are not primarily our own. Even the 3 patients seen by us (Nos. 57, 86, 110), were seen in consultation after several other physicians had already been consulted by the attending physician.

The Fatalities. The conservative physician ordinarily is reluctant to employ unfamiliar therapeutic measures, particularly if they are believed to be dangerous, until he has exhausted his usual remedies and is compelled to recognize that he is confronted with a desperate or practically hopeless situation. This attitude has been

correct, in our opinion. It is repeatedly and indeed almost uniformly exemplified in the series of 100 cases here presented. We hope, however, that future patients may be given the chance of help offered by intravenous bacteriophage without too great delay after staphylococcus invasion of the blood stream has been recognized. In the present series, several patients died before the bacteriophage was actually used in treatment. In others the course of bacteriophage treatment was interrupted or its use was such as to leave something to be desired. Brief notes on some of these unfortunate cases follow.

No. 26, E. P., a woman, aged 26, was delivered of a macerated fetus on July 16, 1932. Blood cultures taken on July 17 and July 22 yielded *S. aureus*, 80 colonies per cc. of blood on the latter date. On July 26 there was a severe chill and her physician requested bacteriophage which was promptly furnished. However, when the bacteriophage arrived the "patient did not seem very ill and other consultants would not permit phage therapy." On the next day hysterectomy was performed. The patient died on August 4.

No. 31, L. B., a girl, aged 8, developed otitis media on September 14, 1932, followed by extensive inflammation of the accessory nasal sinuses. On September 18, the maxillary antrum was opened and portions of turbinate bodies removed. Cultures from the sinuses yielded *S. aureus* but there appears to be no record of a positive blood culture. Bacteriophage was requested on September 23 and was promptly supplied. Intravenous injections of the phage were given: 5 cc. on September 24, 2 cc. on September 25, 4 cc. on the 26th, 5 cc. on the 27th and on the 28th, 15 cc. on the 30th, 10 cc. each on October 1, 2, 3, 4 and 5. Metaphen and Pregl's iodin were also given intravenously and several transfusions were given. The necropsy on October 5 disclosed purulent pachymeningitis, general phlebitis of the dural sinuses with obliteration of the cavernous sinuses, purulent adhesive pericarditis, metastatic abscesses of the heart muscle and of the kidneys.

No. 36, P. S., a boy, aged 16, received a blow on the chest wall about November 2, 1932. On November 15, he was admitted to hospital, irrational, with diagnosis of acute rheumatic fever. On November 16, the spinal fluid contained 10 cells per c.mm., with a trace of globulin; thick pus was aspirated from the chest wall and a blood culture was taken, which yielded *S. aureus* by the next day. Thereupon bacteriophage was requested and intravenous injections started: 0.5 cc. at 11.40 A.M., 1 cc. at 12.10 P.M. Then the thoracic wall was incised and a fractured rib disclosed. Following the operation a dose of 4 cc. of phage was given intravenously at 2 P.M., at which time the patient was evidently failing. At 2.30 P.M. there was no response to stimulation and at 3.46 the patient died. The autopsy presented the picture of general sepsis.

No. 42, M. H., a girl, aged 17, with osteomyelitis of the pelvic bones, invading the hip joint, was relieved of her blood-stream infection following bacteriophage therapy but developed severe secondary infection of the operative wound with hemolytic streptococci and other bacteria and eventually died. Her record has been presented in an earlier paper.[5]

No. 44, V. M., female, aged 21, ill since December 31, 1932, developed local pain and swelling in the left parotid region about January 14, 1933. Upon admission to hospital, January 21, a blood culture was taken which yielded staphylococci. The parotid region was incised and pus found on January 23. Bacteriophage was requested on January 24 and promptly supplied by messenger but the patient died at 1.30 P.M. on this date before the bacteriophage could be used.

No. 45, E. C., a girl, aged 11, had a blood culture taken January 24, 1933, which yielded countless colonies of *S. aureus*. Bacteriophage was requested January 26 and immediately supplied. Some of it was used, but not more than 20 cc., because the remainder was returned to us. Death occurred on January 26 and autopsy disclosed empyema, multiple abscesses in myocardium and osteomyelitis of the right clavicle.

No. 48, C. O., a girl, aged 16, was admitted to hospital with acute left mastoiditis on January 25, 1933, and treated by mastoidectomy on January 28. Bacteriologic findings on material from this operation are not available. Blood culture on February 3 yielded *S. albus*. On February 4 and February 6 blood culture gave negative result. On February 7 the lateral sinus was exposed and the left jugular vein ligated. On February 18 blood culture again gave growth of *S. albus*. Bacteriophage was requested and supplied by us on February 18. A second blood culture, which appears to have remained negative, was taken about 6 P.M. on this day and then the bacteriophage was given intravenously at 6.20 P.M., a dose of 1 cc. and subsequently at intervals of 1 hour doses of 2–6–8–5 cc. up to 10.20 P.M., the total amount being 22 cc. There was no evident reaction. On the next day, February 19, an intravenous dose of 5 cc. was given at 1 P.M. and another of 8 cc. at 2 P.M. There was a chill at 2.25 P.M. On February 20 an intravenous injection of 2 cc. was given at noon and on February 21 at 11.30 A.M., 2 cc., and again at 8 P.M., 2 cc. On February 22 a blood culture was taken, which appears to have remained negative, and then the patient received a series of intravenous injections from 11.25 A.M. to 9.30 P.M., the total amount being 153.5 cc. At 8 P.M. there was some mental confusion but there was no recognized chill. An injection of 5 cc. was given on February 24 and again on February 26 and February 28, but apparently no more phage after that. Transfusions were given: 400 cc. on March 7 and 500 cc. on March 11. On March 11 the jugular bulb was explored. The patient died at 3.55 P.M. March 13. Without wishing to be too critical, one may nevertheless express some skepticism about the validity of the two positive blood cultures in which *S. albus* was recognized. It must also be evident that the clinical application of the bacteriophage lacked precision. This record is presented as an example of lack of sympathetic understanding of bacteriophage therapy and a lack of intelligent clinical application of this agent. We include it among our failures, although we suspect that the patient actually died of a streptococcus mastoiditis complicated by sinus thrombosis. The record of temperature and pulse has not been made available to us.

No. 51, A. R., male, aged 27, had chronic recurrent osteomyelitis with amputation of leg in 1918. He was admitted to hospital on March 3, 1933, and an operation was performed on the femur on April 28. On April 29 at 4 A.M. the temperature reached 106.4 and a blood culture taken at this time yielded *S. albus*. His condition steadily grew worse. Bacteriophage was requested and supplied on May 3 and beginning at 10.45 A.M. on this date a series of 13 intravenous injections was given, the total amount of phage being 75.5 cc. There was no evident reaction. The patient died at 6 A.M., May 4.

No. 55, S. K., female, aged 31, had a furuncle on her chin on June 12, 1933. She was admitted to hospital at 1.45 P.M. on June 16 at which time her temperature was 101.8, rising steadily to 105 at midnight. Blood culture taken on June 16 yielded a growth of staphylococcus on the next day. Bacteriophage was then requested and supplied and at 11.20 A.M. June 17, an intravenous injection of 4 cc. was given. There was no reaction. The patient died at 11.45 A.M.

No. 57, A. N., male, aged 57, developed an abscess near his left knee on June 12, 1933. He was admitted to hospital. A blood culture positive for

S. aureus was obtained on July 8, 1933 and bacteriophage was supplied by us on July 10. On August 4, he was transferred to a second hospital, where the bacteriophage treatment was resumed on August 17 with the specific preparation. The blood culture became negative and on August 24 we were informed that the patient was much improved. Bacteriophage therapy was discontinued on August 31; a note in the record submitted to us a year later says "no more bacteriophage obtainable." The patient died October 8, 1933.

No. 64, H. C., male, aged 41, was admitted to hospital August 28, 1933. Blood culture taken on this day gave positive growth of staphylococcus on August 30. Spinal fluid taken on August 28 was under increased pressure with slight increase of cells, and another spinal fluid taken on August 29 gave a positive growth of staphylococcus. Bacteriophage was requested and supplied on August 31. At this time the neck was rigid and the patient comatose. Intravenous injections were started at 11.50 A.M. and continued until 3.30 P.M., the total amount of phage being 15.5 cc. Death occurred at 4.10 P.M. and autopsy disclosed an acute vegetative endocarditis and embolic abscess of the brain.

No. 69, A. M., male, aged 37, had a small furuncle inside the nostril on the nasal septum on September 14, 1933. The swelling had extended to the forehead and eyelids when he was admitted to hospital on September 19. Record of blood culture has not been given to us but we were informed that the patient had staphylococcus septicemia on September 23, 1933, when the bacteriophage was first requested and immediately supplied by messenger. The patient died before the bacteriophage reached the hospital. The final diagnosis was cavernous sinus thrombosis and meningitis.

No. 73, R. S., female, aged 31, had been under treatment for mastoiditis 4 months. At some time before her last illness she got a splinter in her finger and a felon had developed but this was not treated by a physician. On November 1, 1933 she had a violent headache and was admitted to hospital on November 2. Blood culture taken then was sent to us on November 3 with positive growth of *S. aureus*. Bacteriophage was supplied at once but the patient died on November 3, before any of it was used.

No. 85, E. O., female, aged 24, had a small furuncle on her face on December 24, 1933, which was opened. On December 31 she had a chill and on January 1 her temperature reached 105. She was admitted to hospital on January 6 and a blood culture taken on this day yielded *S. aureus*. The culture was submitted to us on January 9 with request for bacteriophage which was at once supplied. On January 10, intravenous injections of the phage were begun at 4.15 P.M. and continued until 12.25 A.M., the total amount given being 75.5 cc. There was no reaction and the phage therapy was discontinued. The patient died on January 18, 1934 at 1.25 A.M.

No. 87, V. H., a girl, aged 12, had an infected blister on her heel on January 7, 1934. On January 14, she was admitted to hospital with a suppurating left knee joint and osteomyelitis of left femur and left shoulder. Blood culture taken either January 14 or 15 yielded 29 colonies of *S. aureus* per cc. of blood. Bacteriophage was requested on January 25. The intravenous injections were started on this day and continued to January 28, the total amount administered in these 4 days being 90 cc. The attending physician then discontinued the use of bacteriophage. The blood culture taken on January 27 showed 4 bacteria per cc. of blood and that taken on January 31 as well as subsequent blood cultures was negative. Many transfusions were given after January. The patient died on June 20, 1934, nearly 5 months after bacteriophage therapy was discontinued.

No. 93, W. J., male, aged 46, was admitted to hospital on February 26, 1934 and his left kidney was removed on March 1. On March 2 his tem-

perature rose to 102 and on March 19 it reached 105, remaining above 104 thereafter until death. A blood culture, apparently taken on March 19, yielded growth of staphylococcus. Bacteriophage was requested on March 20 and supplied at once. However, none was ever given to the patient. On March 22 an exploratory thoracotomy was done with negative findings. The patient died on March 23.

No. 102, L. S., male, aged 34, suffered a wound of thumb by broken glass on December 24, 1933. A severed tendon was sutured on the same day. Blood culture taken on January 15 was negative but that of January 19 yielded *S. aureus*. Subsequently many positive and some negative blood cultures were obtained. There were 23 operations for drainage of suppurating foci and 30 transfusions. After about 5 months, bacteriophage was requested on June 6, 1934, as a last resort. On this day the patient received 75.5 cc. intravenously in a series of injections. Smaller doses were continued daily until June 13. A blood culture taken June 9 was positive for staphylococcus. Death occurred at 2.30 A.M. on June 15.

No. 106, H. M., male, aged 19, was admitted to hospital on April 30, 1934, with infected hand and diabetes. Blood culture taken on May 7 gave growth of *S. aureus*. The hand was incised on May 9, the arm on May 10, the elbow on May 11 and the arm on May 13. Further operations included chest aspiration and incision of leg on May 19, incision of heel on May 22, incision of forearm on May 26, aspiration of abscess in neck on June 2, incision of buttock on June 4 and incision of arm on June 9. A stock bacteriophage was employed from time to time as follows: May 17, intravenously, 5 cc.; May 26, applied to wounds; May 30, a course of intravenous injections; June 2, local application of 10 cc. to abscess in neck; June 7, a course of intravenous injections with shock and temperature rise to 106. Our service was requested on June 23 and on the next day our stock bacteriophage was given in a series of intravenous injections to a total amount of 41.5 cc. Small injections were given on June 27 and July 2. Specific bacteriophage was prepared as rapidly as possible but with unusual difficulty and delay. It was finally ready but did not reach the bedside of the patient (Philadelphia) in time to be used. The patient died July 3, 1934.

No. 113, R. M., male, aged 15, had pain in his abdomen, right hip and right thigh upon awakening August 2, 1934. He was admitted to hospital on August 3. Blood culture, taken apparently on August 4, gave positive growth of *S. aureus*. On August 6 an intravenous injection of 20 cc. of 1% mercurochrome was given. Later on this same day bacteriophage was requested and the stock asparagin preparation was given intravenously in divided doses to a total amount of 29.5 cc. followed by chill and temperature rise to 106.8. On the next morning the temperature was 99. Contrary to our advice, another series of intravenous doses was administered to a total of 19.5 cc. with chill and temperature rise to 105.2. On August 8 a third series to a total of 59.5 cc. was given without reaction. The patient appeared better and the temperature was lower. Blood cultures, however, remained positive. Bacteriophage therapy was then discontinued. A series of irradiated transfusions was given from August 9 to August 16. On August 17 bacteriophage injections were started again and given daily in large amounts: 70.5 cc. on August 17, 19.5 cc. on August 18, 60.5 cc. on August 19, 80 cc. on August 20, 20 cc. on August 21 and 20 cc. on August 22. The patient died at 11.45 P.M., August 23.

It is, perhaps, essential to emphasize the fact that these patients were not under our control. We have supplied bacteriophage upon request to any qualified physician who furnished reasonably reliable evidence that his patient had a staphylococcus bacteremia. Along

with this we have included advice in regard to use of this agent, which may or may not have been followed. We have earnestly requested that the positive blood culture, preferably one of the original plates, be delivered to us at the earliest possible moment and that we be furnished with a record of the case upon its completion. We are very grateful indeed for the records which have been provided by the different physicians and hospital executives. Without these this discussion would not be possible. For scientific purposes, it is perhaps fortunate that there has been such a lack of uniform practice in using the bacteriophage. One thus has presented a variety of contrasts in therapy and also some contrasts in results. Such records of past experience guide a future course through similar problems.

The few selected fatalities briefly reviewed above illustrate some of the most marked departures from the method of treatment which we recommend. In some instances a more fortunate therapeutic program might have led to a better outcome. We hesitate to pass judgment however. Certain it is that many patients in the series succumbed to the disease even though the treatment represents the best of which we possess knowledge. One has to recognize that staphylococcus bacteremia is a disease of high mortality and that in many instances it has already passed beyond human control before the diagnosis is made.

Comment. The appraisal of a therapeutic agent on the basis of clinical experience is beset with difficulty. The human material is lacking in uniformity. One takes the patients as they come. It has been suggested that alternate patients might be observed as controls, intentionally omitting the use of bacteriophage. Such a program would require a control of the clinical material which we have lacked. Furthermore, we should be loath to attempt such a control series even if the clinical material were available under our control. One occasionally hears that in staphylococcus bacteremia the death rate without bacteriophage is only about 50%, but one does not find the recorded observations on which such a loose statement may be based. Apparently those who have observed such recoveries have been satisfied to make their diagnoses on clinical evidence only or upon a single positive report of growth of staphylococcus of undetermined variety in a flask of broth, or in some instances without any distinct attempt to identify the sort of microbe present in the blood culture. Previous to the use of bacteriophage our observations of staphylococcus infection of the blood stream, proven by reliable blood cultures, had made us believe that recovery was extremely rare.

Though each individual in this series has presented peculiar features, nevertheless there are several which may be placed in a control group, not by our intent, but by circumstances wholly beyond our influence. For Patient 26, for example, the bacterio-

phage was supplied but not used, apparently because she was not regarded as sick enough to warrant it. Patients 44, 69, 73, 93 died before any bacteriophage was used. Patient 51 died within 20 hours after beginning use of the phage, which produced no recognizable reaction. Patient 64 was comatose when the bacteriophage was started and died 4 hours later without reaction. In 2 instances (Patients 26 and 93), the clinical condition upon arrival of the bacteriophage was good enough to allow further operative incision. In the other 5, the disease had already reached a clinically hopeless stage. These 7 may properly be regarded as controls.

In the discussion of the fatalities there are mentioned 12 other patients whose records indicate inadequate use of bacteriophage or complicating factors in the disease or in the therapeutic measures employed. In some of these the bacteriophage was discontinued after clinical improvement and the disease again progressed to death, as for example Nos. 57, 87 and 114.

In the group of 25 survivals, Patient 100 appears not to have been helped by the bacteriophage and in fact there is good reason to doubt the existence of staphylococcus bacteremia in this case. Patient 74 did not receive any bacteriophage and the evidence of a blood stream infection in this case seems to be quite inadequate. The remaining 23 patients who recovered seem to have received benefit from the bacteriophage and in several of these the effect may properly be said to have been life-saving.

Summary. 1. Staphylococcus septicemia occurs in both sexes and at all ages but during adult life is somewhat more common in males.

2. Brief notes are presented on 100 cases, No. 16 to No. 115 in our series of staphylococcus bacteremias receiving our bacteriophage service. Of these patients 75 died and 25 survived. This is a much better percentage than is found in published reports of this condition.

3. Staphylococcus infection of the blood stream is definitely influenced by the intravenous administration of potent bacteriophage and when wisely employed the bacteriophage is helpful, sometimes even life-saving in the treatment of these patients.

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CLINICAL AND ELECTROCARDIOGRAPHIC PICTURE OF CORONARY OCCLUSION PRODUCED BY RUPTURED ANEURYSM OF THE ABDOMINAL AORTA.

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Much has been written on the differential diagnosis of coronary occlusion, especially in regard to the accuracy with which this condition may mimic acute abdominal disturbances. Lately, attention has been called to the antithetical problem of misinterpreting acute abdominal symptomatology as coronary disease.[1] The electrocardiogram is an invaluable aid in this differentiation if used with a knowledge of its limitations. Occasionally it is unchanged in coronary occlusion. The following report demonstrates the opposite situation, namely, that electrocardiographic changes typical of coronary occlusion may occur in the absence of that accident.

Case Report. A white man, aged 59, was first seen on January 17, 1934, complaining of headache and fatigue. He had had scarlet fever in childhood and a cholecystectomy for gall stones 9 years before. There were dyspnea on slight exertion and a history of 3 attacks of auricular fibrillation in the last 3 years. On physical examination, the pulse rate was 112, and the blood pressure was 165 systolic and 120 diastolic. There was a soft systolic blow localized over the precordium. In addition, there were moderate exophthalmos and lid lag. The left pupil was slightly larger than the right, though both were round and reacted to light. The knee jerks were active. Orthodiagraphic measurements were: transverse cardiac diameter, 13.9 cm.; transverse diameter of the chest, 26 cm. The thoracic portion of the aorta was slightly ectatic. The Kahn test of the blood was negative. The basal metabolic rate was +1%; other laboratory procedures were uninformative.

On April 27, 1934, he was brought to the Cottage Hospital in an ambulance from a bath house on the beach, where he had been picked up unconscious. He was in coma and extremely dyspneic. The systolic arterial pressure was 50; the diastolic, 40. The radial pulse was weak and at times unobtainable. The apex heart rate was 120 and the sounds were distant but regular. Râles were heard at the bases of the lungs posteriorly. The remainder of the examination, including the abdomen and reflexes, was not remarkable. A catheterized urine specimen was free of sugar and acetone bodies.

An electrocardiogram was strikingly changed as compared with a previous one (Fig. 1) taken, January 17, 1934, in which the only abnormality was pronounced left-axis deviation. On the new tracing obtained 2½ hours after hospital entry (Fig. 2), there was a rate of 90, disappearance of the left-axis deviation, an extremely high take-off of the *T* waves in Leads 2 and 3, and a normal Lead 4 as obtained by chest electrodes. This is a "*T*3" type of tracing,[2] showing the changes frequently encountered in recent coronary occlusion and suggesting that the infarcted area is near the base of the heart.

Death occurred a few hours after hospital entry. The clinical diagnosis was acute coronary occlusion.

Necropsy (11 hours after death): The abdominal part of the aorta was dilated to a circumference of 13 cm. from a point 12 cm. proximal to the bifurcation and extending distally into the origins of the common iliac arteries. There was a transverse rupture, 5 cm. in length, of the posterior part of the wall, 10 cm. proximal to the bifurcation, with extensive retroperitoneal hemorrhage. The aortic wall was thickened throughout this region, the intima being friable, and mottled with yellow and white plaques, but containing little lime. The heart weighed 500 gm. and was unchanged

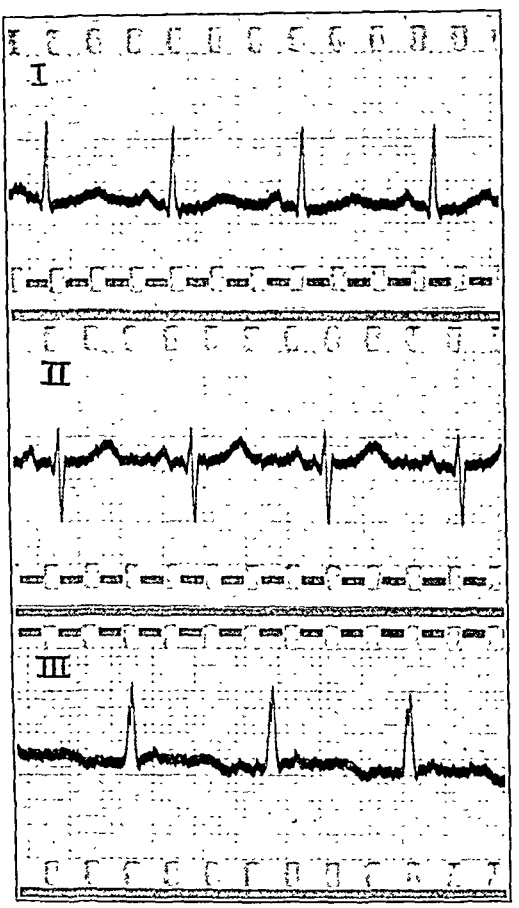


FIG. 1.—Electrocardiogram taken 3 months before death.

except for pronounced thickening of the walls of the coronary arteries. This was particularly true of the descending branch of the left and of the main stem of the right. The lumens were patent throughout, though in places considerably narrowed. The myocardium everywhere was red-brown, and especially careful search failed to reveal any scars or areas of softening. In sections of the aorta, moderate thickening of the intima with fibrous tissue was seen, as well as the characteristic syphilitic changes of perivascular round-cell infiltration of the adventitia and media. In sections from several portions of the myocardium, the muscle fibers were widened and stained well. There was no fibrosis.

Comment. To our knowledge, the diagnosis of ruptured aneurysm of the abdominal part of the aorta has not previously been confused with coronary occlusion. Usually, the prominent symptom of low

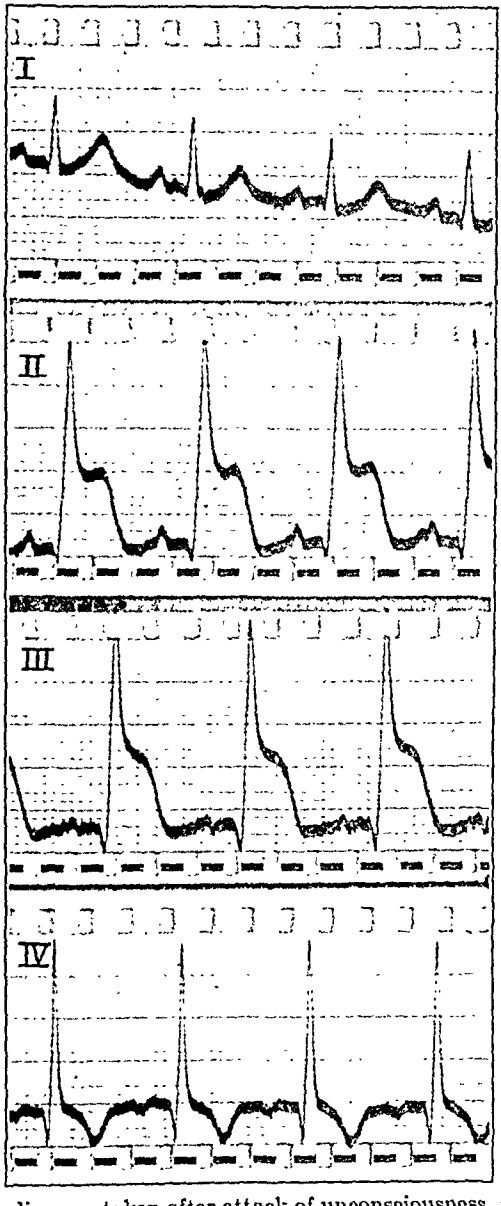


FIG. 2.—Electrocardiogram taken after attack of unconsciousness, a few hours before death.

back pain serves to focus the attention away from the heart and, while the diagnosis may not at first be evident, acute cardiac disease need not be considered.

White *et al.*[3] have recently reported a case of dissecting aneurysm of the thoracic part of the aorta wrongly diagnosed as coronary occlusion. In retrospect, they explain that the correct diagnosis should have been suggested by the lack of sufficient electrocardiographic abnormality. This is particularly interesting to us, as in this case we were confronted with typical electrocardiographic evidence, apparently confirming the erroneous diagnosis of coronary occlusion.

Acute changes in the *R–T* and *S–T* segments of the electrocardiogram are associated (*a*) with a sudden disturbance of the metabolism of the heart mediated through changes of certain of the constituents of the blood, and (*b*) with sudden partial or total deprivation of the blood supply to a portion of the myocardium. To the first group belongs the changes associated with various toxemias, such as pneumonia[4] and uremia,[5] in which the *T* waves have been noted to be of the coronary type. Likewise here are classified the electrocardiographic alterations encountered in diabetic coma (Faulkner and Hamilton)[6] and insulin shock, or in the abrupt but less serious fluctuations of blood-sugar level, dependent upon improper treatment. In diabetes, according to Soskin *et al.*,[7] the storage and/or utilization of glycogen is interfered with. Following excessive doses of insulin, the energy production of the heart muscle is handicapped because of the too rapid lowering of the blood sugar and depletion of the supply. Hence, the final effect of too little or too much insulin is similar. Decreased amplitude and increased slurring of the *Q–R–S* complexes and a tendency of the *S–T* segment and *T* wave to shift in a direction opposite to the major initial complex were noted. Siegel[8] has likewise shown that, if the production of lactic acid from its precursors, sugar and glycogen is interfered with (as in diabetes), the *T* waves become flattened.

Finally, to this first group may be added the observations of Katz *et al.*,[9] who found that general anoxemia in normal persons produced diminution in the amplitude of the *T* waves, at times leading to inversion, without the occurrence of pain. At the same time the *S–T* segment became depressed. Similar changes were found in patients with angina pectoris, of whom 2 out of 6 had mild pain.

As regards the second group, the electrocardiographic changes of coronary occlusion are well known. The ischemia may be relative as a discrepancy between the demands of the heart and its blood supply (Lewis[10]), or absolute when a portion of the myocardium is totally deprived of its circulation. The lumens of thickened coronary arteries may be adequate to provide sufficient nourishment for a heart beating at a normal rate, but inadequate for the same heart speeded up by exercise, thyrotoxicosis, fever, etc.

In the present instance, the explanation appears to be that, though the coronary arteries had considerably thickened walls, they supplied enough blood to the heart muscle to prevent anginal symptoms and electrocardiographic changes. Following the hemorrhage, however, with attendant reduction of the circulating blood volume and shock, the myocardium was no longer adequately nourished, as demonstrated by the second electrocardiogram. The thickened coronary arteries probably contributed to this effect, and, had the patient lived longer, gross changes of softening might have been recognized in the heart.

Summary. An instance is reported of ruptured aneurysm of the abdominal part of the aorta in which, because of coma, the subjective symptomatology could not be obtained. The clinical picture strongly suggested shock following coronary occlusion. Electrocardiographic changes, which were characteristic of and before death were diagnosed as those of coronary occlusion, are seen in retrospect to have been probably due to a relative ischemia of the myocardium without infarction. This ischemia depended on thickened coronary arteries and the reduced circulating blood volume following hemorrhage.

We wish to thank Dr. Franklin R. Nuzum for permission to report this case.

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PERSISTENT PAIN IN THE SHOULDER REGION FOLLOWING MYOCARDIAL INFARCTION.

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The material presented in this report consists of 14 cases in which more or less constant and persistent pain in the shoulder region developed within a period of 4 months after acute myocardial infarction. In 3 cases the shoulder pain developed almost coincidentally with the acute attack and in 4 other cases within a period of 4 weeks. In the other 7 cases the pain developed 1 to 4 months after the acute attack. The diagnosis of myocardial infarction in all cases was confirmed by electrocardiograms including both limb and chest leads. In 11 of the 14, tracings were made during both the early and late stages of infarction; in 3 during the late stage only.

Case Reports. Case 1.—P. M., a white male, aged 52, developed acute infarction of the anterior or apical portion of the left ventricle on May 29, 1933. The acute pain centered in the upper part of the chest and first radiated down the left arm and later down both arms. He remained in the hospital for 25 days, during which time he developed continuous pain in the left shoulder region, which radiated down the left arm. Movement of the shoulder, although not restricted, caused temporary increase of the pain.

Six months after the initial attack he suffered another attack with pain similar to the first. Thereafter the pains in the left shoulder and arm increased. Since that time he has been subject to anginal attacks, and although the distribution of pain is similar to that of the continuous pain, he states that the anginal pain is different. He could not describe the difference, except that the one pain was continuous and the other paroxysmal. The anginal pains, however, were promptly relieved by the inhalation of amyl nitrite. During the 3 months following the second acute attack, the continuous shoulder pain became worse and a so-called "trigger zone" developed over the upper part of the left scapula, pressure over which caused knifelike pain in the left shoulder, left breast and down the left arm.

Neurologic examination by Dr. William G. Spiller failed to reveal any evidence of spinal cord disease. Spinal fluid examination was normal. Roentgen ray of the left shoulder was negative; of the spine showed slight lipping of the bodies of the vertebræ. Irradiation therapy of the upper spine and left shoulder region was instituted but not completed, since he insisted on discharge from the hospital. On his way home he suffered a circulatory collapse, but recovered from this attack. Later he reported that he was somewhat improved, attributing the improvement to the irradiation. However, he still suffered considerable pain.

CASE 2.—S. S., a white male, aged 62, on May 16, 1929, was suddenly stricken with severe pain across the front of the chest, radiating to the left arm, the neck and the back. A diagnosis of coronary occlusion was made and he was kept in bed 16 weeks. When first seen by one of us (J. E.) in October, 1929, he complained of attacks of severe substernal pain, radiating down the left arm, up to the neck and to the back, provoked by exertion, excitement or talking too much. An electrocardiogram made at that time showed inversion of T-2 and T-3 and a deep Q II and Q III. About this time he first noted continuous pain in the left shoulder and discovered that pressure over the upper portion of the left scapula produced a pain which radiated to the left shoulder, down the left arm and up the left side of the neck. The pain produced by pressure over the scapula was similar to the pain of the attacks provoked by exertion or excitement, except that it was less intense and did not radiate to the anterior portion of the chest.

He was again seen in October, 1934. The shoulder pain had continued throughout the entire 5-year period, being of about the same grade of severity despite many different types of treatment. Movement of the shoulder was not impaired. The trigger zone persisted throughout the entire period. The anginal attacks, however, were more easily provoked by exertion or excitement than 5 years previously. Roentgen ray of his spine (cervical and dorsal) and left shoulder failed to reveal any abnormalities.

CASE 3.—D. S., a white male, aged 55, had attended the Medical Outpatient Section of this hospital since April 6, 1931. The diagnosis made was emphysema and chronic bronchitis. Following an absence of several months, he returned to the section on January 12, 1933, complaining of pain of 3 months' duration in the shoulder joints, much more marked on the left. The pain was severe, constant, burning in character, and extended down to the left elbow and also over the left pectoral region. Examination of the left shoulder revealed nothing except some restriction of motion. The pain dated from a cardiac attack in which he was, in his own words, "saved from expiring by the attention of a private physician who gave him needles in his left arm." He also complained of occasional attacks of paroxysmal dyspnea, accompanied by severe substernal pain radiating to the left shoulder. Following these attacks the pain in the shoulder was increased in intensity. His electrocardiogram was of the type found in the healed stage of infarction of the posterior wall of the left ventricle. The shoulder pain had decreased somewhat by May, 1933. He was seen again, November 3, 1934, when the pain had entirely disappeared.

CASE 4.—M. L., a white male, aged 58, was in fair health until July 12, 1933. Beginning at that time, he had a succession of three attacks thought to be due to coronary occlusion. The pain centered over the precordial area and radiated down the left arm. He was kept at rest for 3 months and returned to work on October 15, 1933. On November 11, he had an attack of coronary occlusion which caused grave circulatory collapse. As in the earlier attacks the pain was greatest in the precordial area and radiated down the left arm. An electrocardiogram revealed the presence of recent infarction involving the anterior wall of the left ventricle. He was kept in bed for 6 weeks. He gradually regained his strength and had no complaints until the early part of February, 1934. At that time he began to complain of pain, greatest in the region of the left biceps muscle, but also involving the left shoulder. The pain was constant, of an aching character and radiated down the left arm. It was worse at night, requiring sedatives. Examination showed restriction in motion of the arm posteriorly but no tenderness over the joint or muscle. Roentgen ray examination of the left shoulder, humerus and cervical and upper dorsal spine, failed to

disclose any abnormality sufficient to account for his pain. Many abscessed teeth were found which were later removed. Smears of prostatic secretion contained about 25 leukocytes per high-power field and prostatic massage was instituted. These measures as well as diathermy and baking were apparently without effect. He received deep Roentgen ray therapy to the cervical and upper dorsal regions on November 10, 1934. Improvement was noted after several days and complete relief occurred in 3 weeks.

CASE 5.—W. F. A., a white male, aged 48, was admitted to this hospital (service of Dr. Stengel) on February 13, 1934, 2 days after the onset of a severe attack of coronary occlusion, with severe pain in the substernal area radiating to the precordium. An electrocardiogram revealed the presence of acute infarction involving the posterior wall of the left ventricle. Although at the time of admission, he was critically ill, he improved fairly rapidly and insisted on leaving the hospital on February 21, 1934. He was next seen on October 8, 1934, by our colleague, Dr. F. C. Wood. At that time he felt fairly well at rest; however, exertion or excitement produced a heavy tearing discomfort in upper sternal region. He tired easily but had no dyspnea. He had suffered a constant pain, "like a wrench," in the left shoulder, which had begun while he was confined to bed during the acute attack 8 months before. The pain had recently shifted from the left to the right shoulder.

CASE 6.—W. J. R., a white male, aged 44, was seen in consultation September 17, 1934. On July 31, 1934, he had an attack which was diagnosed acute coronary occlusion. The diagnosis was confirmed by electrocardiogram. His acute pain began in the left shoulder and arm and later involved the substernal region. Since the attack he has had pain in the left shoulder and arm, not relieved by nitroglycerin. The pain is almost constant, but does not prevent him from sleeping and is not affected by moving the arm or walking about. There were no points of tenderness along the nerve trunks, nor in the muscles of the shoulder. There was no restriction nor pain on movement of the shoulder. Muscular strength of the shoulder muscles was preserved.

CASE 7.—S. S., a white male, aged 58, was admitted to this hospital (service of Dr. Stengel) July 23, 1932. He had suffered from angina pectoris for a number of years, but on July 21, 1932, had an attack of coronary occlusion with an overpowering feeling of compression of his chest. The electrocardiogram showed infarction of the anterior wall of the left ventricle. Convalescence was uneventful until the first week in August when he developed pain in the left shoulder. The pain increased when he was allowed out of bed and continued as a constant ache in the left shoulder.

A focus of infection was sought. Several abscessed teeth were discovered and removed, apparently without influencing the shoulder pain. Roentgen ray of the shoulder, May 31, 1933, disclosed the following: "There is no evidence of calcified subacromial bursitis on the left, but there is a little calcareous deposit in the right so-called subacromial bursa, best visible with the arm in internal rotation." Roentgen ray of the spine on June 5, 1933, disclosed minimal hypertrophic osteo-arthritic changes about the bodies and articulating processes of the lower cervical and upper dorsal vertebræ. He was given Roentgen ray treatment to the cervical spine but without relief. Roentgen ray treatment directly over the left shoulder was advised but the patient did not return for it. He was again seen in July, 1933, when he still continued to complain of shoulder pain but of diminished intensity. When seen August 27, 1933, the pain had disappeared. On October 16, 1933, there was another attack of coronary occlusion with infarction of the posterior wall of the left ventricle. This attack was not followed by shoulder pain. Death occurred suddenly on August 25, 1935.

Extensive ancient infarction of both anterior and posterior walls of the left ventricle was found at necropsy.

CASE 8.—E. Q., a white female, aged 53, had been known to have hypertension for 13 years. In 1930 she suffered a severe attack of pain in the arms followed by unconsciousness. Coronary occlusion was suspected, but an electrocardiogram made several months later by one of us (C. C. W.) was normal. Another tracing made in 1932 showed minor changes but no evidence of myocardial infarction. On August 25, 1933, there was an attack of violent pain in the left shoulder region radiating to the neck and down the left arm to the finger tips. A tracing made 4 months later showed the healed stage of infarction of the anterior wall of the left ventricle. Following this violent attack, she was subject to attacks of angina pectoris provoked by exertion and relieved by nitroglycerin. The pain which began August 25, 1933, according to the patient, never disappeared entirely. Furthermore, the radiation to the neck and down the left arm to the finger tips persisted. This pain was considerably aggravated by her attacks of angina pectoris. Various types of medication appeared to be without effect on the shoulder pain, although as stated above, the angina pectoris was promptly relieved by nitroglycerin. Roentgen ray of the cervical spine and left shoulder, November 8, 1934, showed "hypertrophic changes involving the anterior lip of the lower cervical vertebræ: the left shoulder was negative." Death occurred suddenly on January 21, 1935.

CASE 9.—B. D., a white female, aged 58, was admitted to this hospital (service of Dr. Stengel) on March 25, 1934, 2 days after the onset of a severe attack of coronary occlusion. The acute pain was chiefly in the epigastric region. The electrocardiogram showed evidence of recent infarction of the anterior type. Her Wassermann reaction was positive. In addition to the regimen for the treatment of acute coronary occlusion, mercury and iodids were given. Her course in the hospital for a time was stormy, due to pain and congestive failure. By the early part of June these had cleared up. In the latter part of June, however, she developed pain in the right deltoid muscle which gradually shifted to the right shoulder region. From here the pain radiated to the bend of the elbow and occasionally down to the finger tips. No tenderness was present except during times when the pain was exceedingly severe. She was seen again on October 13, 1934, at which time she felt fairly well except for the pain in the right shoulder. Roentgen ray examination showed bilateral cervical ribs.

She was readmitted to the hospital on November 21, 1934, in a state of acute shock. The legs were cold, blue and pulseless. Death occurred the same day. Autopsy revealed old and relatively recent areas of infarction of the anterior wall of the left ventricle and a large soft mural thrombus beneath one of these areas. A thrombus completely occluded both iliac vessels. Examination of the cervical ribs disclosed these to be small and apparently not exerting pressure upon the neighboring bloodvessels or nerves.

CASE 10.—H. K., a white male, aged 60, a coppersmith, was in good health until September 25, 1934, when he was seized while at work with a severe agonizing pain over the upper chest, radiating to both shoulders and down both arms to the finger tips. Relief followed several hypodermics of morphin but a sense of numbness remained in the little and ring fingers of his right hand. An electrocardiogram showed evidence of infarction involving the posterior wall of the left ventricle. Convalescence was uneventful except for the very frequent occurrence of "heartburn" not relieved by alkalis. On October 14, 1934, he began to have persistent pain in both shoulders (dull, aching), worse at night and slightly aggravated by motion. The numbness of the two fingers of the right hand persisted. Roentgen ray of the spine and shoulders, taken November 19, 1934, dis-

closed no abnormalities in the cervical and upper dorsal spine or shoulders. Deep Roentgen ray therapy over the upper spine and shoulder instituted November 27, 1934, was without beneficial results.

CASE 11.—L. U., a white male, aged 61, was first seen August 5, 1933. He had been in good health until 3 weeks before, when he experienced substernal pain following a large meal. He then improved rapidly, but on August 1, 1933, was seized with a severe substernal pain which radiated to the right shoulder and down the arm, for which he received 3 hypodermics. When seen on August 5, 1933, he was free from pain but felt very weak. An electrocardiogram showed recent infarction of the anterior wall of the left ventricle. He was ordered to bed and remained there 6 weeks, during which time convalescence was uneventful. However, toward the end of his stay in bed, he complained of a slight, constant pain in the right shoulder. On arising from bed this pain became more severe and radiated down the arm to the finger tips. Substernal pain radiating to the right shoulder also occurred often, especially on exertion or dietary indiscretion. He was seen at frequent intervals until March 13, 1934, but in spite of medication, rest and baking, the shoulder pain continued. The pain gradually subsided and on April 21, 1934, had disappeared. The attacks of substernal pain had also decreased in frequency and severity. Death occurred suddenly on January 5, 1935.

CASE 12.—C. S., a white male, aged 56, was first seen March, 1933. He had suffered attacks of pain in the epigastric region for several years, especially on exertion or excitement. Following business reverses the attacks became more frequent and severe. On March 6, 1933, he was suddenly seized with a severe, agonizing, crushing pain in the upper sternum, radiating down both arms, but especially the left. An electrocardiogram showed evidence of recent infarction involving the anterior wall of the left ventricle. Following the initial pain, convalescence was uneventful until 4 weeks after the onset, when he developed a severe pain in the left shoulder radiating down the arm. The pain was constant, dull, aching and worse at night. Local applications, analgesics and baking failed to give appreciable relief. Roentgen ray of the teeth revealed one abscessed tooth which was subsequently removed. Following the extraction there was no immediate increase or decrease in the intensity of the pain. Four weeks later, or approximately 10 weeks after the onset of the shoulder pain, it decreased in intensity and gradually subsided.

CASE 13.—H. W., a white male, aged 38, an insurance agent, was well until October 29, 1934, when he developed substernal pain radiating to both arms on effort and relieved by rest. The attacks increased in severity and intensity and on November 10 he had a very severe attack while at rest. He was put to bed and on the 4th day, upon arising from bed, he coughed up about 1 ounce of blood-tinged sputum. He was admitted to this hospital (service of Dr. Stengel) November 14, 1934, complaining of a constant, dull pain under the sternum. An electrocardiogram done November 16, 1934, was of the type found in the subacute stage of infarction involving the anterior wall of the left ventricle. Subsequent electrocardiograms showed huge *T* waves in Leads IV and V. Convalescence was uneventful and he was discharged from the hospital January 25, 1935. He was readmitted April 29, 1935. During the interim he had anginal pain and dyspnea on effort. Five weeks before his second admission he began to experience a constant "hot" pain in the right shoulder region made worse by movement of the shoulder, but not aggravated by exertion which did not involve movement of the right shoulder. On this admission he remained in the hospital only a few days. The pain was not relieved at the time of his discharge.

TABLE 1.—MYOCARDIAL INFARCTION AND SHOULDER PAIN.

Case.	Sex.	Age.	Location of infarct.	Shoulder affected.	Time relation of cardiac attack and onset of shoulder pain.	Duration of shoulder pain.	Anginal attacks.	Remarks.
1. P. M.	M	52	Anterior	Left	Less than 25 days	18 months; severity decreased	Severe	"Trigger zone" over upper left scapular region.
2. S. S.	M	62	Posterior	Left	4 months	5 years; no relief	Severe	"Trigger zone" over upper left scapular region; pain worse after attacks of angina.
3. D. S.	M	55	Posterior	Left	Coincident	Over 9 months; complete relief	?	Pain worse during and after attacks of paroxysmal dyspnea.
4. M. L.	M	58	Anterior	Left (biceps)	3 months	10 months; complete relief	No	Shoulder pain increased by excitement or cough; relieved following deep Roentgen ray therapy.
5. W. F. A.	M	48	Posterior	Both	Within a week	Approximately 8 months; no relief	Yes	Pain shifted from left to right shoulder.
6. W. J. R.	M	44	Anterior	Left	Coincident	2 months; no relief	No	
7. S. S.	M	58	Anterior	Both	Approximately 2 weeks	Approximately 1 year; complete relief; sudden death 2 years later	Yes	Posterior infarction over a year after anterior, not followed by shoulder pain.
8. E. Q.	F	53	Anterior	Left	Coincident	17 months; slight relief; sudden death	Yes	Aggravated by excitement; relieved by rest.
9. B. D.	F	58	Anterior	Right	4 months	Until death 5 months later	No	Bilateral cervical ribs; at necropsy found very small and exerting no pressure.
10. H. K.	M	60	Posterior	Both	4 weeks	4 months; no relief	No	Numbness in first and second fingers of right hand.
11. L. U.	M	61	Anterior	Right	Approximately 6 weeks	7 months; complete relief	Mild	Sudden death 8½ months after relief of pain.
12. C. S.	M	56	Anterior	Left	5 weeks	10 weeks; complete relief	Mild	
13. H. W.	M	38	Anterior	Right	4 months	6 weeks; no relief	Mild	
14. S. S.	M	53	Anterior	Left (deltoid)	6 weeks	7 weeks; complete relief	Mild	Pain never severe.

CASE 14.—S. S., a white male, aged 53, was referred for study on April 19, 1935. During the preceding 2 weeks he had noted several transient attacks of substernal pain. On the night of April 17, 1935, he was awakened by severe substernal pain, radiating down the left arm. Following the administration of morphin hypodermically by his physician the pain was relieved but not entirely abolished. Slight pain was still present on April 19, 1935. An electrocardiogram revealed the presence of acute infarction of the anterior wall of the left ventricle. He was kept at complete rest for about 7 weeks during which time there were several transient attacks of substernal pain. About June 1, 1935, he began to note pain in the region of the left deltoid muscle which persisted until about July 20. The pain was not severe but was constant. It did not interfere with movement of the left arm and was not aggravated by movement. There was no tenderness over the deltoid nor shoulder region and no limitation of motion. No sensory changes were noted.

Discussion. *Incidence.* Persistent pain in the should region following myocardial infarction is apparently not an uncommon symptom. However, we were unaware of this relationship until several patients, all of whom had had myocardial infarction, complained bitterly of shoulder pain. Our failure to account for the pain on any conventional basis led to consideration of the possibility that the cardiac lesion might in some way be responsible. For this reason a systematic study of our other available patients who had survived attacks of infarction was made, and a total of 14 cases with persistent shoulder pain was assembled. In all, approximately 100 cases were followed, which suggests that the incidence of this symptom among the survivors of attacks may be over 10%.

The sex, age, location of the infarct (as determined by electrocardiogram), the time of onset of shoulder pain with reference to the acute attack of infarction, the duration of the shoulder pain, the presence or absence of anginal attacks and certain atypical features of the various cases are listed in Table 1.

Character of the Pain. The pain has been described as "burning," "aching," or "wrenching." As a rule the patients had some difficulty in localizing it, often referring it to the general region of the shoulder. In 1 patient, however, the pain was limited to the region of the left deltoid muscle and in another, was greatest over the biceps. In 8, the pain was limited to the left shoulder region, in 3, to the right, while in 3 both shoulders were affected. The pain tended to be continuous, although subject to periods of exacerbation and amelioration. In 2 patients there was a so-called "trigger zone" in the scapular region, pressure over which caused great increase in pain. Those who suffered attacks of angina pectoris had no difficulty in distinguishing them from the shoulder pain, but in a few, the shoulder pain was definitely worse following an attack of angina. In 1 case the shoulder pain was increased during and immediately after attacks of paroxysmal dyspnea.

Time Relation to Acute Cardiac Attacks. The time of onset of the shoulder pain was variable. In 3 of the 14 cases it appeared

to be practically coincidental with the attack of coronary occlusion. The longest interval between occlusion and shoulder pain was 16 weeks after the attack. In a number of cases the pain came on so gradually that the patient could not date it accurately. In all but 4, however, it began within 6 weeks of the attack.

Duration. The duration of the pain in this series of cases varied greatly. In 1 case it was mild and lasted only 7 weeks. At the other extreme is the case in which the pain has persisted for 5 years and still continues. In 6 of the patients pain was still present at the last follow-up examination. Two of the 4 patients who died continued having shoulder pain up to the time of death. Six were relieved of the pain in periods varying from 7 weeks to 12 months.

Possible Non-cardiac Causes. 1. Results of Physical Examination: In most of these patients, physical examination of the shoulder region has proven entirely negative. As a rule, ordinary movement does not aggravate the pain, but in a few patients, pain seemed to be increased by exaggerated movements of the shoulder. Except for the 2 patients with so-called "trigger zones" over the back of the shoulder, no tenderness on pressure was elicited in the region of the shoulder, arm or back. There appeared to be no impairment of strength of the shoulder muscles, no atrophy, and no sensory changes. No vasomotor changes were noted and no differences in the pulses on the two sides were found. The occurrence of periarthritis of the shoulder, in cases with cardiac pain, has been reported by Howard.[1] We were, however, unable to find evidence of periarthritis in any of our cases.

2. Roentgen Ray Examinations: Roentgen ray studies of the shoulders and spine were made in 7 of the more severe cases. In 6 the shoulders were entirely negative. In 1 there was a slight calcareous deposit in the right subacromial region, but the left, which was the painful shoulder, showed no abnormality on Roentgen ray examination. In 3 cases slight lipping of the bodies of the vertebræ was found, not sufficient to be considered abnormal for this age group. In 1 case, however, Roentgen ray of the chest disclosed bilateral cervical ribs, but at necropsy these were found to be quite small and apparently incapable of exerting pressure on neighboring bloodvessels or nerve trunks.

Results of Treatment. Treatment for the relief of pain was singularly ineffective. The ordinary analgesics (not including opiates), nitrites, baking, diathermy and removal of foci of infection appeared to be without material influence. In 1 case deep Roentgen ray therapy seemed to relieve pain; in 1 it gave a questionable result, but in 2 others it was ineffective.

Analogy of the Pain to Causalgia. The time relations of the onset of pain to attacks of coronary occlusion, and its peculiar characteristics, which tend to differentiate it from the well recognized forms of shoulder pain, suggest that it is related to the cardiac lesion and referred from the heart. It should be stated, however,

that in most cases there was recognized no significant correspondence in location between stenocardiac types of pain and the shoulder pain. In a few cases, however, there did appear to be some correspondence.

It occurred to us that the shoulder pain bears a closer analogy to causalgia than any other recognized type of pain, although the trophic and vasomotor changes associated with causalgia have not been observed in our cases. Furthermore, hyperesthesia was present in only 2 cases.

Pollock and Davis[2] have recently stated that the pathogenesis as well as the pathology of causalgia is unknown. These authors, however, associate causalgia with peripheral nerve injuries. Leriche[3] believes that periarterial sympathetics play an important part in the production of causalgia and that such lesions as obliteration of an artery or inclusion of sympathetic fibers in a scar may provoke the syndrome. In support of his hypothesis he has been able to bring about complete relief in most of his cases by periarterial sympathectomy. In some cases, however, it was necessary to resect the obliterated artery in order to obtain relief.

Whether or not under the term causalgia more than one entity is included need not concern us here. Our interest is in the fact apparently demonstrated by Leriche that obliteration of an artery may cause causalgia. Leriche's studies have dealt with peripheral arteries. However, the characteristics of the shoulder pain as it occurred in our patients as well as its refractoriness to treatment bear such a close analogy to the pains which may develop after block of a peripheral artery that a similar mechanism of pain production is suggested. No additional evidence is available at present to support this view. The operation of cervico-thoracic sympathectomy might throw some light on the question as to whether the sympathetics are concerned in production of the pain. However, we have not thus far felt warranted in suggesting this operation to any of our patients. Consequently the analogy of the pain to causalgia is suggested for the following reasons only: (1) the similarity of the pain to causalgia and (2) the time relationship of onset of the pain to occlusion of a coronary artery. The chief purpose of this report is not to discuss the pathogenesis of the pain, but rather to call attention to the fact that it is to be recognized as a sequel to coronary occlusion.

Although this study has been limited to a consideration of cases in which shoulder pain developed following myocardial infarction, there is some evidence to indicate that a broader relationship may exist. Thus, since we have become interested in this subject, we have encountered 1 patient with persistent burning pain in the interscapular region and another with a persistent sensation of warmth and at times burning in the left forearm, following coronary occlusion. Moreover, shoulder pain of the type described above has occasionally been complained of by patients with severe myo-

cardial damage, in whom no evidence of infarction could be recognized.

Summary. 1. Fourteen cases with persistent pain in the shoulder region following myocardial infarction have been briefly described. It is suggested that the incidence of this symptom among survivors from infarction may exceed 10%.

2. The pain may be mild or severe and was usually described as burning, aching or wrenching. The left shoulder is usually involved, although the right may also be affected. The pain may shift from one shoulder to the other. Occasionally the pain may be greatest in the region of the biceps or deltoid muscles.

3. It may begin coincidentally with an attack of coronary occlusion up to at least 16 weeks after the attack.

4. The pain persisted from 7 weeks to over 5 years.

5. Local treatment to the shoulder has proven ineffective. Deep Roentgen ray therapy has been tried in several cases without consistent results.

6. Most patients in this group had foci of infection. A few had slight cervical or upper dorsal spondylitis. Nevertheless, the frequency of occurrence after myocardial infarction and the time relations to the attacks, suggest that the cardiac lesion is an important etiologic factor. An analogy to causalgia is suggested.

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ACETYL-β-METHYLCHOLIN.

IV. Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm.

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Many derivatives of cholin, administered to animal preparations, produce effects on the heart analogous to those which follow stimulation of the vagus.* [19] By means of acetyl-β-methylcholin this

* Since 1925 paroxysmal tachycardia has been occasionally stopped by intravenous injections of cholin chlorid (Bohnenkamp, Klin. Wchnschr, 14, 404, 1935). Stepp and Schliephake (Münch. med. Wchnschr, 72, 1997, 1925) also reported a case of "paroxysmal tachycardia" in which unnamed "cholin derivatives" caused increased block. The ekg. given suggests auricular flutter.

effect can be produced in the clinic to a degree not yet attained by other means. The therapeutic utility of the cardiac action of this drug will be considered in this paper. The drug also produces the other effects of parasympathetic stimulation: vasodilatation, saliva-

Both Professor Hunt[10] and Professor Villaret[11] and their associates had published animal experiments in which a drug was employed under the name of acetyl-α-methylcholin. That this drug had been erroneously named did not occur to us in 1933.

Following Simonart's publication,[12] Hunt took the position that what he had described as acetyl-α-methylcholin was in reality acetyl-β-methylcholin.[13,20] Professor Villaret[14] suspected that what he had used might have been a mixture of acetyl-α- and acetyl-β-methylcholins. The latter view is concurred in by Simonart,[16] who finds acetyl-α-methylcholin to be a much weaker drug than the β compound. Later Villaret adopted Hunt's point of view.[15]

After using what he then believed to be a mixture, in 1932, Villaret *et al.*[14] published an article, entitled "Preliminary Researches Concerning the Action of Methyl Acetyl Cholin in Normal Subjects." This antedated our first publication, reaching our attention when it was in press. After doses of 10 to 30 mg. of the bromid, Villaret recorded flushing and effects on the blood pressure of 12 normal subjects which corresponded in a general way with results we obtained using the acetyl-β-methylcholin chlorid made by Major and Cline's method. But the absence of any record of sweating, of salivation and of changes in cardiac rate and respiratory depth, so conspicuous after similar doses in our experiments, made us doubt whether the drug used by Villaret, made by Morley's method, could have been the same as that we employed, made by the method of Major and Cline. A further difference in results seemed to be indicated by the following statement: "Nous avons établi qu'en installations conjonctivales la méthylacétylcholine déterminait rapidement un myosis intense, et que, fait très intéressant, seule entre tous les myotiques actuellement connus, elle arrivait à vaincre aisément la dilatation pupillaire provoquée par l'éphédrine. In another paper,[21] speaking of the action of 1 or 2 drops of the misnamed acetyl-α-methylcholin in the rabbit's eye he wrote: "Il faut, cependant, utiliser les concentrations de l'ordre de 5 p. 100, ou, mieux encore, de 10 p. 100, pour voir apparaître, en deux à quatre minutes, un myosis qui est maximum en quatre à sept minutes, avec pupille réduite à un orifice de 1 millimètre environ; cet effet commence à diminuer après 45 à 60 minutes, pour persister, atténué, jusqu'à deux heures après l'instillation."

Hunt obtained similar results with his misnamed acetyl-α-methylcholin on the pupils of dogs and cats. He wrote: "One drop of a 3% solution caused an intense constriction within 5 to 10 minutes; this continued undiminished for about 15 minutes."[10]

I have repeated these experiments as closely as possible with Major's acetyl-β-methylcholin chlorid. In 3 brown rabbits slight pupillary constriction was always seen after 1 or 2 drops of 10% solution. In the most striking experiment the pupil diminished from 6 to 4 mm. diameter and so became 2 mm. smaller than the opposite pupil. In 3 white rabbits 2 drops of 10% caused the pupil to diminish from 10 to 8.5 mm. in one animal, it had less effect in the other two, although enough was absorbed to cause salivation in each instance.

Dr. Schmidt has failed to obtain myosis in cats using repeated applications of 1%,[16] and I could not demonstrate noteworthy myosis after 1 drop of 3% in three cats.

When stronger solutions are applied to the conjunction with sufficient frequency some myosis can be regularly obtained together with evidence of systemic action. But we have never seen anything which is at all similar to the effects described by Hunt and by Villaret after the doses they employed. But it should be pointed out that we have not repeated the experiments of the latter author, for the European rabbit differs from the American.

The drug used by Hunt and by Villaret in these early experiments was described as a "unique" myotic causing "intense constriction" after small doses. Pure acetyl-β-methylcholin has only a weak myotic action; marked pupillary effects have not been seen without increasing the dosage to the point of inducing systemic effects. There is also chemical and other pharmacologic evidence that the two were not identical.[16, 17] But that Hunt and Villaret were employing an active cholin derivative with features in common with acetyl-β-methylcholin is not disputed.

tion, sweating, increased gastro-intestinal motility, etc., as have been described.[1] When small doses are given to animals and to normal persons the blood pressure falls but the vagus-like action does not manifest itself. After large doses this effect appears.[2] It cannot be produced without the simultaneous occurrence of a fall in blood pressure and the other effects mentioned above to such a degree that the subject is made distinctly uncomfortable for a few minutes. However, after a subcutaneous injection of acetyl-β-methylcholin, the intensity of the action remains under the control of the attending physician. This fact has made possible the utilization of a type of drug action more vigorous than is usual in clinical medicine.

In an earlier communication[2] (1933) the results obtained in the treatment of 29 attacks of paroxysmal tachycardia in 9 patients were reported. At present, data are available on 75 such attacks, in 36 patients, treated by acetyl-β-methylcholin with success in 88%. Six cases of auricular flutter have also been treated, but with only occasional success in restoring normal rhythm. In 1 case with ventricular extrasystoles the number of premature beats was markedly reduced by the drug. In auricular fibrillation no change in the rhythm has been brought about.

Additional clinical experience has added to our knowledge of the drug and has afforded an explanation for some of the failures reported. One can now draw a clearer picture of the best method of securing results with acetyl-β-methylcholin in the cardiac arrhythmias, of its probable effectiveness when thus employed, and of its untoward effects, than was possible a few years ago.

Paroxysmal Auricular or Supraventricular Tachycardia. Electrocardiograms demonstrating the arrhythmia to be of this type were secured in only 20 of the 37 patients, but clinical criteria permitted little doubt that the attacks of the remainder were of the same type. These data (Table 1) can be considered best by dividing them into

TABLE 1.—DATA ON EFFECT OF ACETYL-β-METHYLCHOLIN ON PAROXYSMAL TACHYCARDIA.

	Philadelphia.	Other.	Total.
Number of patients	17	20	37
Attacks treated	50	25	75
Attacks stopped	46	20	66
Failures	4	5	9
Per cent success	92	80	88
Successful from drug action alone on first trial	58%		
Required carotid sinus pressure during drug's action	20%		
Required second, usually larger, dose of drug	22%		

two groups: The Philadelphia group contains my own experience together with a small number of other cases treated at the University Hospital in my absence but in accordance with a plan I devised.

This is a selected group because carotid sinus pressure failed to stop the attack in each case included. The second group contains data sent me by friends in other cities. I am especially indebted to Dr. H. M. Korns, of Iowa City, Dr. J. M. Hayman, of Cleveland, Dr. H. M. Marvin, of New Haven, and Dr. D. N. Kremer and Dr. F. W. Burge, of Philadelphia, for very full reports of their experiences. The attacks of many patients in this group could not be stopped by carotid pressure, but in others this was not tried, and in a few instances I lack the information.

The Philadelphia cases were treated as follows. The patients lay down. Alternate pressure over the carotid sinuses was tried first. This was successful in 16 instances, and these cases have been eliminated from this study. When carotid sinus pressure was unsuccessful the drug* was given subcutaneously. If the attack did not stop promptly after the appearance of the flush, the site of the injection was vigorously massaged to increase the action. In 26 instances (58%) the attack was brought to an end by these means alone. If tachycardia persisted, the carotid sinuses were compressed alternately while the action of the drug was still undiminished. Frequently the attack stopped as soon as one of the sinuses was touched. In 9 instances (18%) the attack was terminated by carotid pressure during the drug's action, although similar pressure before its administration had been ineffective.

If tachycardia still persisted, about ½ hour was allowed for the drug's effects to subside. Then a second, usually a larger, dose was given, and the procedure repeated. The second attempt was successful in 10 cases (22%). But this does not mean that one should expect the first attempt to fail in a corresponding number of cases. For, in order to estimate the smallest effective dose, we often purposely gave an initial dose so small that there was little expectation of success.

In 4 instances we failed to effect a prolonged restoration of normal rhythm, and I have information concerning 5 other failures. Before the reason for these failures can be discussed profitably, certain information derived from the data must be considered.

Relation of Dose to Age and Weight. The first study suggested that 30 mg. was the proper dose for paroxysmal tachycardia. A dose of this size has been successful in patients under 52 years, but it has failed more often than it has succeeded in older patients Fig. 1). In a boy, aged 18, the attack was stopped by 10 mg., and the side effects were just as intense as those which followed the injection of the 50 mg. regularly required to stop attacks in a man aged 60.

The line drawn on Fig. 1 gives a rough idea of the dose which experience indicates may be expected to stop tachycardia at different

* We are indebted to Merck & Co. for supplying the acetyl-β-methylcholin chlorid used.

ages in patients of normal weight. Some of the most divergent points can be explained on the basis of unusual weight, *e. g.*, 60 mg. was required for an extremely fat man aged 42; 20 mg. was successful in a thin woman aged 58. Other divergent points may have been due to poor selection of dosage. Thus, in 2 instances, young people were given 30 and 35 mg. with success; we do not know that smaller doses would not have been equally effective.

Obviously larger doses are usually required in older people than in young ones. It is incorrect to assign a single dose for all cases

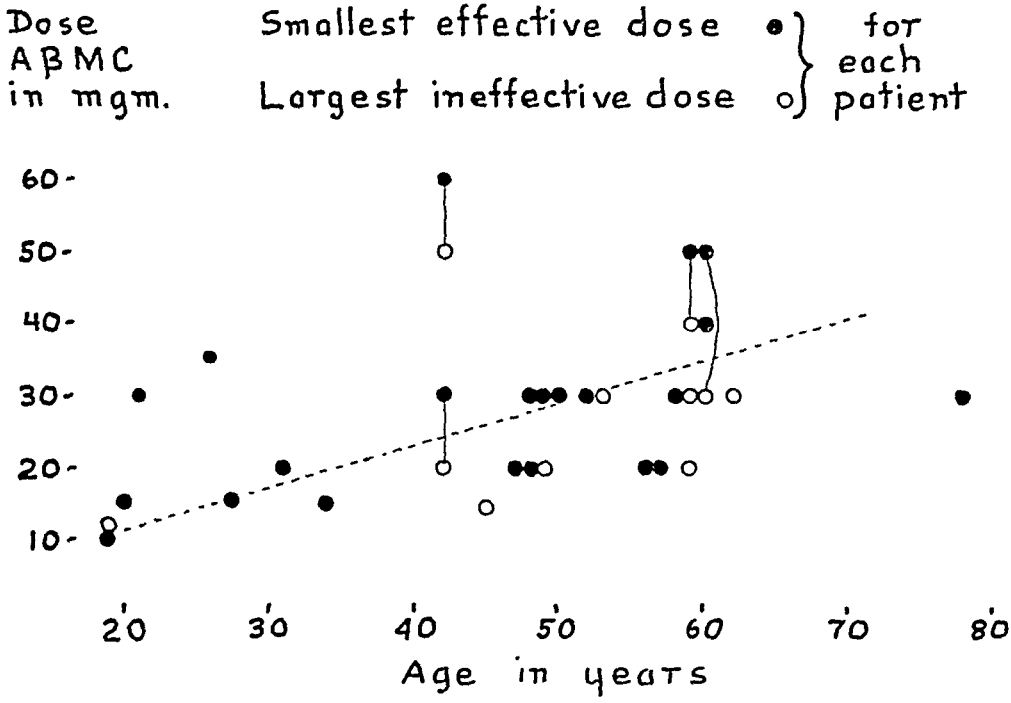


FIG. 1.—Effect of age on the dose of acetyl-β-methylcholin necessary to stop attacks of paroxysmal tachycardia. Only the *largest dose which failed* to stop an attack and the *smallest dose which succeeded* in any 1 patient have been given. Two points which apply to the same patient have been connected by lines. In many cases one or the other of these points is unknown.

of paroxysmal tachycardia. That young persons react to the drug more vigorously than older ones has been the experience of Page[3] also.

Antagonism Between Cardiac Action of Acetyl-β-Methylcholin and Quinidin. The latter drug is well known to diminish the frequency of attacks of paroxysmal tachycardia in certain cases, though it has no reputation as an agent to bring such attacks to an end. Therefore, it appeared worthwhile to ascertain whether a combination of the two drugs' actions might not be advantageous in stopping attacks.

Soon after this idea had presented itself, a patient appeared in tachycardia whose previous attack had been promptly brought to an end by an injection of 30 mg. of acetyl-β-methylcholin. I gave him 20 mg., expecting that it would prove too little, without affecting the rhythm. He was then given 0.67 gm. quinidin by mouth; this was followed by a glass of water, and he was instructed to lie on his right side; a procedure which has regularly procured quinidin action within ½ hour, in my experience. This time having elapsed, the patient received a second dose of 20 mg. acetyl-β-methylcholin in the hope that, reinforced by the quinidin, it might stop the attack. It failed to do so. Doses of 30 and, later, 50 mg. acetyl-β-methylcholin failed also, although they produced the usual side effects. Therefore, the outcome suggested that, far from making the attack easier to stop, quinidin antagonized the usual cardiac effect of acetyl-β-methylcholin.

The opportunity to repeat a clinical observation of this type coming but rarely, it seemed wise to investigate the relationship between the cardiac effects of quinidin and acetyl-β-methylcholin in animal experiments. The results indicated that an antagonism between the cardiac effects of these two drugs could be easily demonstrated.[4]

On the other hand, in 5 instances, patients receiving small doses of quinidin, the largest 0.2 gm., 4 times a day, have had attacks successfully stopped by acetyl-β-methylcholin. The cardiac action of large doses of acetyl-β-methylcholin will break through the quinidin block both in the clinic and in animal experiments.

Causes of Failure to Stop Attacks of Paroxysmal Tachycardia. The chief cause of failure has been too small dosage of acetyl-β-methylcholin. In 10 attacks, in 4 patients, this was proved to be the case when a second and larger dose, given after the effect of the first had subsided, was immediately successful. In 2 instances, both early in our experience and mentioned before, we did not increase the dose and failed to bring the attack to an end. One of these, a patient with ulcerative colitis, received only 12 mg. He vomited and defecated after this dose, and the physician in charge did not try a larger one. As other attacks were stopped by 15 and 20 mg., the failure mentioned is to be attributed to inadequate dosage. In 2 patients, treated in another city by doses of 20 mg., the failure is probably to be assigned to the same reason. Dosage of this size will seldom stop attacks in the latter half of life.

In 3 instances the failure may be assigned to previous medication with quinidin. One patient, given quinidin experimentally, has been discussed above. Another of our patients (C. M. K.) had received 0.5 gm. quinidin and 1 gm. digitalis before treatment with acetyl-β-methylcholin. But we did not give over 15 mg. of the latter drug, which caused transient complete block without stopping the attack. The failure might be assigned to inadequate dosage for

his age, to quinidin, or to an unknown factor. He had received too many active drugs to permit accurate analysis. Complete block, lasting over a few beats, has never been produced in any other of our patients.

In a case of Dr. H. M. Marvin, the patient had been taking 0.6 gm. quinidin sulphate, 3 times a day, for many months. She had taken 2 such doses the morning of the attack, and it was not stopped by 30 mg. of acetyl-β-methylcholin. The quinidin may certainly have been the cause of failure in this instance.

One case of my own and 2 other cases still lack a clear reason for failure. The former deserves brief mention.

A young girl, aged 22, came to me with the history that she had an attack of tachycardia whenever a young man invited her to go to a dance. The attack in which she presented herself was attributed to this cause. The electrocardiogram showed it to be of the supraventricular type. During the action of 20 mg. acetyl-β-methylcholin the attack stopped, as judged by heart sounds, but it resumed promptly. While the drug's action continued, it could be stopped immediately by carotid sinus pressure on either side and by having the patient take a deep breath and hold it; but the rhythm always reverted to tachycardia within ½ minute. A second and third dose of 25 mg. had the same effect. The attack stopped at least 20 times, but it always resumed within a minute; so I admitted defeat eventually. It stopped spontaneously 10 hours later, at almost the exact time the dance was over. I have no explanation of the failure other than to point out my inability to remove the cause of the attacks in this instance.

Attempts to Stop Attacks of Paroxysmal Tachycardia by Other Methods. Seeking for a better method of stopping attacks, I have tried, unsuccessfully, an injection of 30 mg. of the ethyl ether of β-methylcholin and, in another instance, 0.5 mg. of carbaminoylcholin (doryl or lentin). Trying to minimize the side effects I having given an adequate dose of acetyl-β-methylcholin dissolved in ethyl lactate to slow the action, and I have injected the drug together with 0.6 mg. atropin. The side effects were diminished in both cases, but the attacks were not stopped. In each instance, after allowing the effects of the injected drugs to subside, the attacks were promptly stopped by acetyl-β-methylcholin, given in the usual manner.

Dr. Korns has informed me that he successfully stopped an attack of paroxysmal tachycardia by an intravenous injection of 20 mg. acetyl-β-methylcholin without undue toxic effects. The patient's condition, carcinoma of the throat, justified the risk taken.

Auricular Flutter. I have data on only 6 cases of this arrhythmia who were given the drug on 12 occasions. Four cases were my own, and in 3 electrocardiograms were secured throughout the drug's action. I am indebted to Dr. Korns for permission to mention his experience in 2 others.

Temporary slowing of the ventricular rate was secured in all 6 cases by large doses of the drug, 60, 40 or 30 mg. The electrocardiogram showed the slowing to be due to increased block.

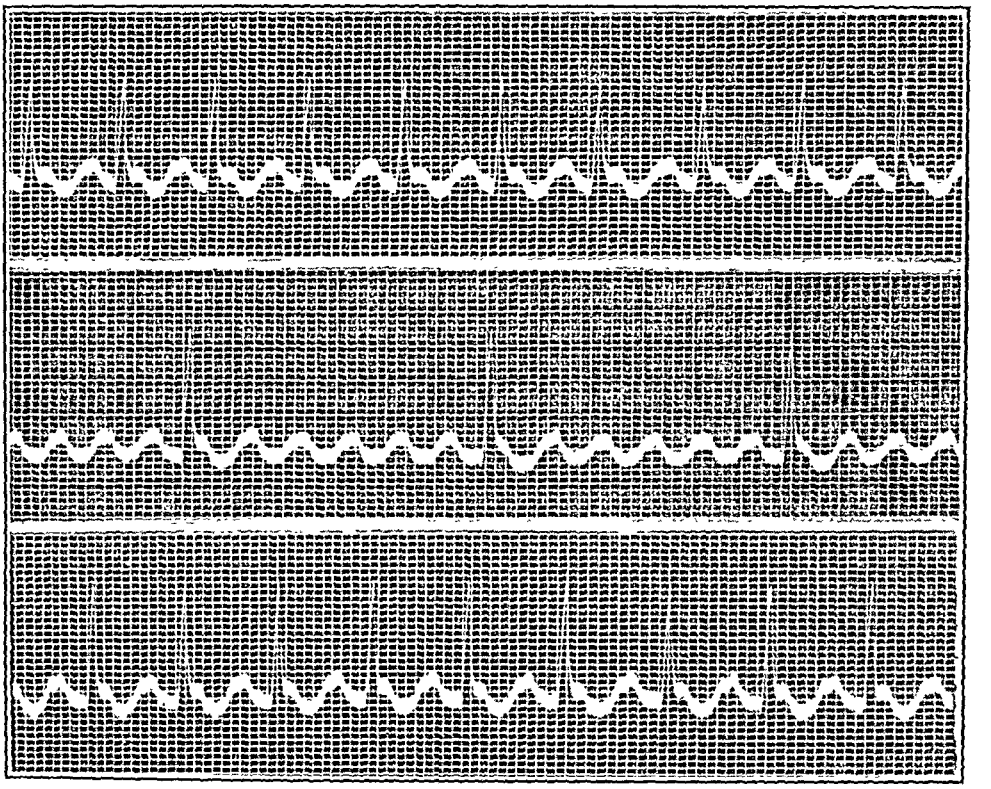


FIG. 2.—Effect of acetyl-β-methylcholin on auricular flutter. Lead II: The upper tracing was taken before, the middle 2 minutes after, the lower 25 minutes after the subcutaneous injection of 44 mg. acetyl-β-methylcholin.

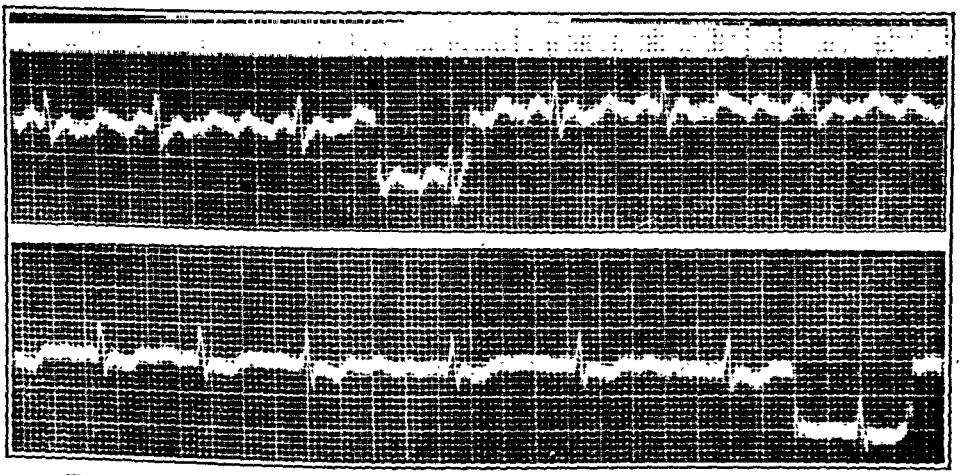


FIG. 3.—Effect of acetyl-β-methylcholin on auricular flutter. Lead II: The upper tracing was taken 2 minutes before, the lower 4½ minutes after a subcutaneous injection of 40 mg. acetyl-β-methylcholin. The patient was under the influence of digitalis.

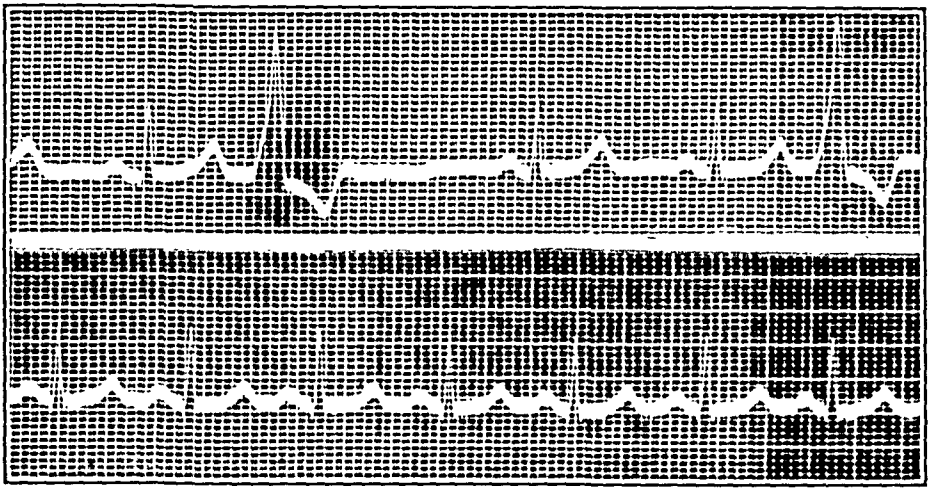


FIG. 4.—Effect of acetyl-β-methylcholin on ventricular extrasystoles. Lead II: The upper tracing was taken 2 minutes before, the lower 5 minutes after a subcutaneous injection of 20 mg. acetyl-β-methylcholin.

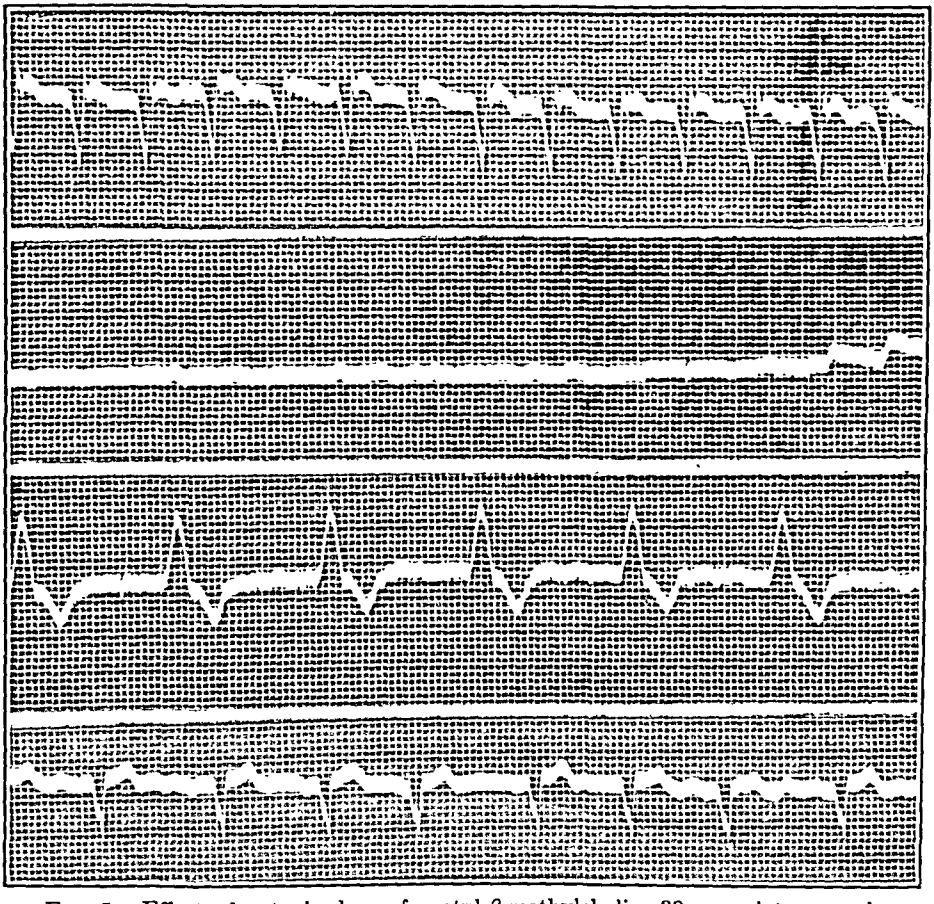


FIG. 5.—Effect of a toxic dose of acetyl-β-methylcholin, 30 mg., *intravenously*. Lead II: The upper tracing was taken before the injection, the second is typical of the record obtained during the next 70 seconds. The third and fourth show successive phases of recovery.

Figure 2 shows such an effect. After the drug's action had passed off the original rate was resumed. Change in the auricular rate was not recorded except in the case mentioned below.

More permanent effects were seen in 2 instances. One patient, with advanced rheumatic heart disease and congestive failure, was given 30 mg. The auricular rate remained constant at 226. The ventricular rate changed from 100 to 120, then to 114; the relation between the adjacent *P* and *Q* waves, inconstant before the drug, became fixed after it at 2 to 1 block. She was then placed on digitalis, without alteration in the flutter, until nausea and vomiting forced us to withdraw the drug 10 days later. Two days after this she was given 40 mg. acetyl-β-methylcholin, and during the action the auricular rate rose from 230 to 300 and then the rhythm changed to auricular fibrillation (Fig. 3). Digitalis was withheld and fibrillation was succeeded by normal rhythm 4 days later. This gratifying result did not produce the expected clinical improvement. Not long afterward the patient developed a hemiplegia and eventually died. Necropsy was not permitted.

Nahum and Hoff[22] have reported a case similarly converted from flutter to fibrillation. Their patient was also under the influence of digitalis when acetyl-β-methylcholin was given. Normal rhythm returned 1½ hours later.

Dr. Korns converted 1 of his cases from flutter to normal rhythm by a dose of 50 mg. acetyl-β-methylcholin. Whether the heart went through fibrillation is unknown. Six months later the same patient had another attack. Four injections, ranging from 40 to 60 mg., had no effect on the auricular flutter in this instance. Normal rhythm returned spontaneously some hours after the last dose.

Auricular Fibrillation. No permanent effects have followed the administration of acetyl-β-methylcholin in this condition. A temporary effect, slowing of the ventricular rate, was seen in most instances, but seemed too transient to be of therapeutic importance. As restoration of normal rhythm was not expected from theoretical considerations, and as nothing of therapeutic importance was gained in the first 10 cases, we have not continued the study of this group.

Nahum and Hoff have produced transient auricular fibrillation by giving large doses to cases of thyrotoxicosis.[22]

Ventricular Extrasystoles. Only 1 case has appeared with extrasystoles in sufficient number to make a study possible.

The patient, an Italian male, aged 50, had many vague complaints for which no satisfactory diagnosis was ever suggested. On the first occasion he was having an extrasystole which replaced every third beat with perfect regularity. An electrocardiogram taken for 5 minutes showed no deviation. After an injection of 30 mg. acetyl-β-methylcholin the extrasystoles greatly diminished in frequency, large numbers of normal beats occurring between them (Fig. 4). They were never entirely abolished and no ½-minute

period occurred without an extrasystole. When the drug's action subsided the original condition returned.

The next day the extrasystoles were found to be replacing every fourth normal beat with perfect regularity. A dose of 70 mg. of the ethyl ether of β-methylcholin was given by mouth. Flushing, sweating and salivation appeared about 1 hour later. At this time the extrasystoles lost their regularity and occurred, on the average, at a ratio of 1 to 8 normal beats. Atropin sulphate, gr. $\frac{1}{150}$, subcutaneously, was given to abolish the cholin action, and within 3 minutes the extrasystoles returned to their original condition, replacing every fourth beat.

On another day the extrasystoles again replaced every third normal beat. The patient was given 1 gm. of acetyl-β-methylcholin, by mouth. Flushing and salivation appeared about ½ hour later. At this time the extrasystoles had diminished to an average of of 1 to 5 normal beats. But on this occasion atropin did not entirely restore the original condition for, after its administration, while the extrasystoles usually replaced every third beat, occasional runs of 3 or 4 normal beats were heard.

Toxic Effects. The Effect of Overdosage. I have been permitted to cite certain instances when misunderstanding of orders resulted in overdosage.

A man, aged 71, had arteriosclerotic heart disease and auricular fibrillation; 30 mg. acetyl-β-methylcholin were administered *intravenously* instead of subcutaneously as directed (Fig. 5). The heart was arrested immediately and this persisted for 70 seconds, a fact of no little interest in itself. The patient lost consciousness. Atropin was administered. The ventricle resumed beating with evidence of an intraventricular conduction defect. The patient revived and within 20 minutes felt as well as before. The conduction defect soon disappeared, but the electrocardiogram remained very different from that present before the drug was given.

In another instance a man, aged 61, with auricular flutter, received 300 mg. subcutaneously instead of 30 mg. There was prolonged cardiac arrest and consciousness was lost. Atropin was administered, the heart resumed beating, and recovery was complete within a few minutes.

In both these instances the atropin could hardly have left the site of injection until cardiac action resumed. Therefore, initial recovery is not to be attributed to atropin, but rather to the well-known physiologic principle: vagus stimulation will stop the heart's action, but the heart will soon escape and resume beating even though stimulation is continued.

Cardiac Arrest Not Due to Overdosage. A situation quite similar to those mentioned above has occurred after a small dose of the drug under the following conditions.

Patient, W. S., aged 19, had ulcerative colitis and marked anemia as well as attacks of paroxysmal tachycardia. While in the hospital 3 attacks were stopped by doses of 10, 15 and 20 mg. acetyl-β-methylcholin. On

each occasion the patient had an irresistible defecation at the height of the action; a pan was provided so that he could remain lying down until action had subsided. After discharge he had another attack of tachycardia and the attending physician injected 10 mg. without provision for defecation. Therefore, when the action began, the patient leaped out of bed to go to the toilet, but soon after attaining the upright position he collapsed, and no heart sounds could be heard. The boy revived within a few minutes and there were no after effects. Atropin was not administered.

The physiologic explanation of this incident seems reasonably clear. Any drug or other situation which lowers blood pressure is likely to cause fainting if the subject is in the upright position. Part of the physiologic mechanism of the fainting reaction is analogous to the response to vagus stimulation; the heart is materially slowed or it may stop for a brief period.[5,6] In this incident the fall in blood pressure due to acetyl-β-methylcholin, together with the patient's lack of hemoglobin, caused cerebral anemia as soon as he took the upright position. The vagus-like effects of fainting and of the drug summated and caused cardiac arrest similar to that seen after gross overdosage.

Patients must be kept in the horizontal position during the action of acetyl-β-methylcholin.

Of the minor toxic manifestations, little has been encountered which was not mentioned in the previous communications,[1,2] but some additional information is at hand.

Asthmatic attacks promptly follow an injection of the drug in patients subject to this disease. This does not occur in other patients, but a sense of tightness across the chest is often complained of and is doubtless due to the bronchoconstrictor action demonstrated in animals by Comroe and Starr,[8] and its result, a decrease in vital capacity, demonstrated to occur in normal men by Hurtado and Kaltreider.[7] Villaret *et al.*[9] have made more extensive observations on this effect of the drug, producing typical attacks in 20 cases of asthma and in 1 patient, convalescent from pneumonia, who had never had asthma.

Substernal pain, or pain referred to the precordium, has followed the administration of the drug on rare occasions. The most striking examples of this were in 2 cases of advanced Buerger's disease with amputations for gangrene. In 1 of these, a patient of Dr. Kremer, it repeatedly followed the injection of 10 and 15 mg. I can only speculate as to its origin. The location of the pain and the well-known frequency of coronary sclerosis in organic peripheral vascular disease suggest that it might have arisen from the heart. But many other arteriosclerotic persons have received much larger doses of this drug without inducing this symptom.

The coronary action of acetyl-β-methylcholin is not identical in different preparations. In perfused isolated rabbit hearts the drug had usually only a slight effect on the coronary vessels. In 6 such preparations dilatation was regularly seen in 3, constriction pre-

dominated in 2, and there was no noteworthy effect in the other. In the cat, decreased flow was the rule after certain dosage, although mixed effects were sometimes seen.[8] Therefore, the animal experiments have not provided a firm basis for predicting how the drug acts on human coronary vessels.

Another possible explanation is spasm of the esophagus or cardia. I have seen a surprising increase of esophageal peristalsis under the fluoroscope after certain cholin derivatives. While I have never experienced precordial discomfort after an injection of acetyl-β-methylcholin, I have had a dull epigastric and substernal ache after taking another cholin derivative, doryl. This seemed to me to arise from the stomach.

This type of toxic response is very rare in its severe form. Dull precordial or substernal sensations, sometimes spoken of as pain, occur more frequently. Atropin relieves both types immediately, a fact which at once differentiates the drug effect from typical angina pectoris. Nevertheless it seems wise to use this active drug with caution in cases of angina pectoris until more data have been accumulated.

Nausea and vomiting occur occasionally after the drug. I think of them as being the first symptoms of overdosage. In most instances the full cardiac effect of the drug can be attained without these symptoms, but occasionally, as when the patient has recently been nauseated, they occur after moderate dosage.

On the Question of Chronic Toxicity. Nothing has appeared which suggests that harm may result from the prolonged use of this very active drug. In support of this statement it is desirable to report the case who has received a far larger amount of the drug subcutaneously than any other person.

T. H., an elevator operator, aged 58, in May, 1931, gave a history of attacks of paroxysmal tachycardia for 11 years. For the first 10 years he had usually been able to stop the attacks himself, but more recently he had lost this ability and they were increasing in frequency and duration. He denied dyspnea on exertion except during the attacks. Physical examination showed some cardiac enlargement, slight arteriosclerosis, dental and tonsilar infection. Basal metabolic rate was normal. Repeated electrocardiograms showed auricular tachycardia; when not in an attack the electrocardiogram was essentially negative. The cardiac area by orthodiagram was 43% above the predicted normal.

Throughout his illness he had frequently received quinidin, digitalis and phenobarbital in varying dosage in unsuccessful attempts to prevent the attacks.

During his first year in the Outpatient Department several attacks were stopped by carotid sinus pressure, but this method often failed. The frequency and severity of attacks gradually increased until they came on at least every 3 or 4 days, and lasted from 10 hours to 4 days. He became almost completely incapacitated.

In May, 1932, he began to receive injections of acetyl-β-methylcholin for attacks which could not be stopped by other means. Large doses proved necessary. Table 2 shows the date and amount of the injections.

During the fall and winter of 1932–1933 the attacks became more frequent and more prolonged. It became impossible to stop them by carotid or ocular pressure alone. Indeed, they stopped spontaneously very infrequently. But acetyl-β-methylcholin, in doses of 50 mg., continued to be effective, sometimes by itself, more often in combination with carotid pressure.

TABLE 2.—ACETYL-β-METHYLCHOLIN GIVEN TO T. H., 1932–1934.

1932:		1933:		1933:	
May 19	10 mg.	Jan. 4	50 mg.	June	
	20 "	7	50 "	14	50 mg.
	30 "	17	50 "		50 "
	40 "	Feb. 7	50 "	24	50 "
26	40 "	Mar. 4	30 "	July 14	50 "
July 15	50 "		50 "	Aug. 7	50 "
Oct. 11	50 "	13	50 "	8	50 "
15	50 "	14	40 "		50 "
18	50 "	22	50 "	10	50 "
27	50 "	April 28	40 "	1934:	
Nov. 17	50 "	May 15	30 "	Feb. 12	50 "
21	50 "		50 "		
25	50 "	June 9	50 "	*Total:*	
Dec. 1	50 "		50 "	40 injections.	
17	50 "			1.83 gm.	
30	50 "				
	50 "				

At the height of these symptoms he went into auricular flutter and remained in this rhythm for about 2 weeks. This led to admission to the ward, where tonsillectomy and dental extractions were performed. During the flutter, acetyl-β-methylcholin caused transient slowing of the ventricular rate but never changed the rhythm. He has had one brief attack of flutter since that time.

After spontaneous recovery from flutter he again had frequent attacks of paroxysmal tachycardia and appeared for an injection whenever he had a bad one. Though a second injection was occasionally necessary we were invariably able to stop the attacks. Carotid pressure alone gradually became more effective and the injections less necessary.

During the summer of 1933 he regained the power to stop some of the attacks himself, a thing he had been unable to accomplish for well over a year. Since February, 1934, he has not needed assistance. At present his attacks occur infrequently, and he soon brings them to an end by taking a deep breath and bending over. His heart area, which increased to +71% above predicted normal at the height of his symptoms, has now diminished to +27%. His general health is excellent, but it has seemed wise to limit his exertion somewhat. He is not working, being unable to find suitable employment. He is taking 0.3 gm. quinidin and 30 mg. of digitalis 3 times a day at present.

Discussion. *Toxic Effects and Their Relation to Syncope.* No evidence has appeared that acetyl-β-methylcholin is dangerous when administered in a proper manner and dosage. The fatal dose has not been reached; doses of 10 times the therapeutic have led to reactions, alarming but transient. Repeated doses have been administered without the development of any signs of chronic toxicity.

There is a striking similarity between the symptoms produced by an overdose of acetyl-β-methylcholin and the ordinary syncopal

attack. No case of the former has been observed with sufficient care to ascertain the order of development of the symptoms in those cases in which cardiac arrest and unconsciousness supervened; the state of mind of the attending physicians was not conducive to careful observation at that moment. But from a knowledge of the effects of smaller doses the picture can be put together. Objective symptoms common to the action of this drug and to syncope are fall in blood pressure, hyperpnea, sweating, salivation, nausea (occasionally vomiting), increase in pulse rate and, later, pronounced diminution of pulse rate.[6] In both there is prompt recovery without after effects. Atropin immediately relieves both.[5] All of the usual symptoms which follow an injection of acetyl-β-methylcholin have been described in certain cases of syncope. This is a striking analogy.

Certain obvious discrepancies may be explained by differences in position. After acetyl-β-methylcholin, given with the subject horizontal, the face always flushes; in syncope, the patient being in the upright position before collapse, flushing is sometimes seen, but pallor is more usual. In a general vasodilatation with the head raised the blood would be expected to drain into the dependent vessels, leaving those of the face empty; when the head is down, the vessels of the face would remain full. Flushing of the face was seen by Cotton and Lewis,[5] when, after syncope, the subject lay on the floor, and in other patients whose mild attacks did not progress to loss of consciousness.

Page[3] has pointed out the resemblance of the action of acetyl-β-methylcholin to that which follows the injection of pituitrin and pilocarpin into the lateral ventricles. He has also called attention to attacks occurring spontaneously in certain cases of hypertension, which resemble the action of acetyl-β-methylcholin in many of their features.[18] But in these cases the blood pressure rose, a feature I have seen very infrequently after acetyl-β-methylcholin, and much more often after acetylcholin.

It would be of great interest to test the blood of patients exhibiting such symptoms for derivatives of cholin. But, as the animal preparations necessary must be set up in advance, the test will be difficult to attain until a subject is found who will faint, or have an attack, on demand.

Relationship to Other Drugs Commonly Used in Cardiac Cases. Digitalis and quinidin are so often administered to patients with types of arrhythmia treated with acetyl-β-methylcholin that the question of the effect of the former drugs on the cardiac action of the latter frequently arises. The few preliminary pharmacologic experiments[4] have indicated that the cardiac action of acetyl-β-methylcholin may be altered by the other drugs. In my experiments on anesthetized cats and on isolated cat and rabbit hearts, quinidin has regularly diminished the cardiac action of acetyl-β-

methylcholin. But the diminution of the cardiac effect of acetyl-β-methylcholin after quinidin is not to be compared with the complete annulment of all action which follows atropin. Large doses will break through the quinidin effect both in the experimental animal and in the clinic.

The relationship between the actions of acetyl-β-methylcholin and of the digitalis group is more complicated. Pines has demonstrated that the cardiac action of acetylcholin is increased by strophanthin in certain animal experiments.[23] I have obtained a similar result with acetyl-β-methylcholin in isolated rabbits' hearts, and there is a little clinical evidence pointing in the same direction. However, in anesthetized cats and in isolated cat hearts I have not been able to demonstrate this reinforcing effect with any regularity. Also when strophanthin action has progressed to the point of block, or of alterations in the rhythm, doses of acetyl-β-methylcholin, previously effective, may have no effect whatever on the heart's rate. Therefore, my animal experiments have not yet yielded results consistent enough to afford a basis for predicting the effect of digitalis on the clinical action of acetyl-β-methylcholin.

In any event, those using acetyl-β-methylcholin in the clinic must be on the lookout for alterations in its effectiveness on the heart when their patients have been receiving quinidin or digitalis.

Concerning the Use of the Cardiac Action in Therapeutics. As the vagus-like effects of acetyl-β-methylcholin on the heart cannot be secured without a vigorous exhibition of the other actions of the drug, to attain maximum therapeutic results, with a minimum of discomfort to the patient, requires skill on the part of the attending physician. He must not only choose the dose and inject the drug, but he must then control the intensity of the effects. The degree to which the action, after subcutaneous injection, remains under control is surprising. By vigorous massage of the site of the injection it can be intensified; by applying a tourniquet above this site it can be diminished and, at any time, it can be brought to an end immediately by an injection of atropin.

In paroxysmal tachycardia, of the auricular or supraventricular types, an operator skilled in the control of the action and in pressure on the carotid sinuses should bring the attacks to an end immediately in about 90% of instances. The physician who, after the injection, stands idly by, may expect success in a much smaller per cent of cases.

In auricular flutter the drug is only occasionally successful in changing the rhythm. The infrequency with which such patients appear at the clinic and the seriousness of their condition in most instances have hindered the development of a technique which has much promise of success. The transient increase in block, regularly secured, is of no therapeutic importance, but an electrocardiogram taken during it may permit the identification of flutter in some instances hard to distinguish from paroxysmal tachycardia.

Little need be said regarding the advisability of using this very active and, to the patient, disagreeable remedy to stop attacks of paroxysmal tachycardia. The decision must rest on the condition of the individual patient. If the attack can be stopped by a simple mechanical method, as carotid sinus pressure, ocular pressure, etc., such means are to be preferred, although they may produce considerable discomfort in themselves. Patients whose attacks cause them little inconvenience may prefer to be let alone. On the other hand, those who suffer acute distress during attacks usually prefer to have them brought to an end at the cost of temporary discomfort. When experience has taught patients what to expect they find the action of acetyl-β-methylcholin less disagreeable than at the first trial, when the unexpected vigor of the action may frighten them. Several have come for treatment whenever they have had an attack which cannot be stopped by simple means. The rapid transition from the acute discomfort of tachycardia to the well-being which follows the resumption of normal rhythm is one of the striking clinical phenomena.

Summary. Acetyl-β-methylcholin has been used in the treatment of 75 attacks of paroxysmal tachycardia in 37 patients. In 66 instances (88%) the attack was promptly brought to an end.

The dosage necessary to terminate attacks of paroxysmal tachycardia varies with the age as well as with the weight of the patient.

Quinidin antagonizes the cardiac action of acetyl-β-methylcholin and may well be responsible for the failure to bring attacks of paroxysmal tachycardia to an end in certain cases.

In auricular flutter change in the rhythm can occasionally be brought about by acetyl-β-methylcholin.

In 1 case the frequency of ventricular extrasystoles was diminished by the drug.

The effects of overdosage of the drug are described. The symptoms are closely analogous to those of the ordinary attack of syncope.

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LUNG PUNCTURE IN LOBAR PNEUMONIA.

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If lung puncture is to be practised as a diagnostic aid, especially routinely, it should be shown that it is a simple, safe method furnishing useful information. It is the purpose of this report to indicate that the procedure meets these requirements.

Lung puncture was first done by Leyden[1] in 1883. Since then, there are reports or mention of the method by Talamon,[2] Patella,[3] Tchistovitch,[4] Horder,[5] Eyre,[6] Rosenow,[7] Lister,[8] Clough,[9] Abra-

hams, Hallows, Eyre and French,[10] Netter,[11] French,[12] Nuzum, Pilot, Stangl and Bonar,[13] Thomas and Parker,[14] Armstrong,[15] Lyon,[16] Glynn and Digby,[17] Cecil, Baldwin and Larsen,[18] Stewart,[19] Alston and Stewart,[20] Cruickshank,[21] Shibley and Rogers.[22] In a number of these, the matter of lung puncture is only incidental or of minor mention in a paper devoted to another subject. In some instances[2,6,18,22] the punctures were done largely or exclusively postmortem. Lyon's[16] punctures were done entirely on infants and children: 20 of these were lobar pneumonias and 18 bronchopneumonias. Lung puncture studies were also done on influenzal pneumonias. Netter,[11] in the 1918 epidemic, recovered the influenza bacillus in 4 out of 8 lung punctures. Nuzum, Pilot, Stangl and Bonar,[13] in the same influenzal epidemic, did 36 lung punctures but failed to find the influenza bacillus, though the pneumococcus was recovered 11 times.

Most of the lung punctures were done on lobar pneumonias. Smears made directly from the products of lung suction afforded little information of value. Studies were more profitably directed toward the percentage of positive cultures from puncture as well as the number of cases in which the pneumococcus was isolated in purity. Then followed studies on the types in lung puncture cultures and comparison of these results with the sputum findings. Attention was also paid to the stage of the pneumonia in which the pneumococci were recovered and the relation to the crisis, prognosis and virulence. Patella[3] did punctures before and after the crisis finding large numbers of pneumococci before crisis and obtaining inconstant results after crisis. Rosenow[7] noted that while positive cultures were obtained all through the course, the percentage of positive results were much higher in the early stages in favorable cases and tended to diminish in these cases as crisis was approached. On the other hand he found that positive cultures persisted to death in unfavorable cases. Thomas and Parker,[14] in general, confirmed Rosenow's work and showed that where puncture cultures were positive after the sixth day, the mortality was 56% compared with 23.5% in those with positive results up to the sixth day only. They found some cases, however, with positive cultures after the crisis and elaborated a theory of antibacterial and detoxifying mechanisms working independently. The matter of pneumococcic virulence as indicated by the presence of smooth or rough forms and the degradation of S to R forms and their relation to recovery was studied by Shibley and Rogers[22] by lung puncture with somewhat suggestive results, though it would appear that further studies on more cases were necessary for definite conclusions.

The percentage of positive lung puncture cultures in lobar pneumonia during life is, according to various observers, around 50%. Lister[8] in 200 cases got 50% of positives; Thomas and Parker,[14] 59% in 73 cases; Glynn and Digby,[17] 37.5% in 44 cases; Stewart,[19]

76% in 17 cases; Cruickshank,[21] 50%; and Bullowa,[23] about 35% of positives in 1467 cases. The results probably depend on the culture technique as well as the stage and the case of pneumonia. Mostly, pneumococci were found in pure culture, though at times other organisms were also recovered or later contaminated the cultures. The prognostic value of lung puncture has already been indicated in the observations of Rosenow,[7] Thomas and Parker,[14] and Shibley and Rogers.[22] To this may be added the information furnished by typing. In previous studies on lung puncture the typing was confined to the 4 types then recognized. With the 32 or more types now known, and with the utilization of the Neufeld method of typing, the usefulness of lung puncture has, we believe, been extended. It is with this phase that this paper deals.

Lung puncture has never become a popular method of diagnostic approach to pneumonia. The reason for this is almost certainly a hesitancy over a real or apparent danger in the procedure as well as a lack of demonstration of its practical usefulness. Horder[5] as long ago as 1909 published a paper entitled "Lung Puncture: A New Application of Clinical Pathology," a heading which hints at a useful method. Among those who have had considerable experience with lung puncture[12,14,16,17,19] there is general agreement that the danger is negligible. Glynn and Digby[17] in reviewing the subject conclude that "the examination of lung juice in pneumonia is a valuable but neglected aid to exact bacteriologic diagnosis, especially in children. If properly performed, the danger is negligible, except that hemorrhage may occasionally occur." Bullowa,[23] who has had extensive experience with lung puncture, or as he prefers to call it, lung suction, uses the method routinely in a very large pneumonia service at the Harlem Hospital and also finds the danger of no moment in properly selected early cases of lobar pneumonia, employing his technique. He had no increase in empyema, rarely a slight or unimportant hemorrhage and occasionally a pneumothorax. There is unanimity of opinion among observers that there is no increase in the incidence of empyema after lung puncture. Slight transient hemorrhage after puncture is mentioned by a number of writers. Pneumothorax is a rare but real sequel but the present view of its therapeutic value would make it an advantage rather than a disadvantage to the patient. Sudden death is mentioned only once in the references here listed,[14] and must be excessively rare from lung puncture. Collapse or sudden death, following thoracentesis for pleural effusion or lung conditions is said[24] to be due in nearly all cases to air embolism, the point of an unattached, usually large, needle or trocar entering a vein and permitting air suction during inspiration. With the needle firmly attached to a syringe this danger should be eliminated. It is assumed that one's knowledge of anatomy and physical diagnosis will exclude any such unnecessary accidents as puncture of the heart or large vessels or an aneurysm.

Finally improvements in technique, such as the use of a small needle and restriction of any movement of the needle when in the lung, should reduce sequelæ to a minimum.

Technique. In general, after preliminary cleansing of the skin and anesthetization of the underlying tissues with 0.5% procain solution, the consolidated lung is punctured with a long needle attached to a syringe which may or may not contain broth or saline. Strong suction is made, and the resulting withdrawn material distributed to culture media. The skin is usually cleansed with iodin and alcohol. In most cases, local anesthesia is recommended. We did not find it necessary. The needles formerly used were large size and Thomas and Parker[14] employed a 16 gauge. Most operators now advise an 18 to 20 gauge needle. Bullowa[23] uses a very fine, flexible, stainless steel needle, 10 cm. in length, 22 gauge, medium point and 35 degree bevel. The length generally suggested is 10 cm. The syringes advised are of 10 to 20 cc. size. Some use suction as the needle is withdrawn from the lung while others[23] employ suction both as the needle enters and leaves the lung. Thomas and Parker[14] and Stewart[19] use a dry syringe. Glynn and Digby[17] draw 0.5 cc. of saline in the syringe, and after the needle is introduced inject this fluid into the lung and then make steady suction. Bullowa[23] has 3 to 4 cc. of blood broth in the 20 cc. syringe at the time the puncture is made so that the withdrawn material mixes at once with this culture medium. The medium also assists in expelling what remains in the needle. At times, Bullowa[23] finds, some of the contents of the needle may be expelled on a slide for direct typing. Those who use a dry syringe usually rinse out the withdrawn matter with plain, phosphate or glucose broth. The withdrawn lung juice or blood, mixed or unmixed with broth is distributed to culture media such as serum or blood agar plates, blood or chocolate agar slants and broth. Sometimes,[19] a mouse is injected with the broth washings.

The technique we employed was as follows: The location of the consolidated area was carefully located by physical signs and Roentgen ray. Puncture was not done unless there was definite evidence of pneumonia. Over this area of maximum signs and shadow, the puncture was made. This usually was over the posterior inferior aspect of the chest, but we frequently entered the lung without damage through the upper chest posteriorly or anteriorly (infraclavicular region) or in the axilla. The skin over the prospective site was thoroughly swabbed with alcohol only. No anesthetic was used and patients made little or no complaint. A dry 5 cc. glass syringe with a 6 cm. No. 20 needle was employed. The needle was entered 5 or 6 cm. and strong suction made on withdrawal. The needle, after introduction, was not moved about or changed from its primary position in the lung except to withdraw it. If negative pressure was encountered on suction the results were usually good: if positive pressure was found and the piston of the syringe slipped back easily, the results were usually disappointing. Commonly a little bloody matter was obtained. This might be only a drop or two or as much as 1 cc. Not infrequently nothing grossly visible was removed or a mere serous moisture. Occasionally just before complete withdrawal a little clear fluid entered the syringe, evidently a thin pleural exudate. In this instance, positive cultures were not always obtained. After the needle was removed from the lung, the contents of the syringe were at once washed into a single tube of slant agar at the bottom of which were 1.5 cc. of plain broth pH 7. This was done by entering the small 5 cc. syringe and needle into the agar tube so that the needle reached to the bottom of the tube. The broth was then sucked up into the syringe and expelled, and this was repeated 4 or 5 times. Even when there was no visible withdrawn matter the procedure was

followed and positive cultures were not infrequently obtained. Especially was this prospect good if a few fibrin flakes were seen. The tube was at once incubated and examined at short intervals later, say 2, 4, 6 and 12 hours, by making spreads of the broth at the bottom of the slant and the agar surface just above it.

The first evidence of growth, if the examination of the broth was made only a few hours after the puncture, was at times only a few pneumococci. At other times, the first examination showed numerous organisms. After their first appearance, even in very small numbers, the pneumococci increased very rapidly. As soon as they were in sufficient numbers for typing, this was done by the Neufeld method, using a small drop of broth against one or two of serum. A culture was considered ripe for typing when there were at least 10 bacteria per oil-immersion field. Fewer bacteria, when diluted with typing serum and methylene blue, required too tedious a search to find the organisms. Pneumococci cultured this way showed beautiful capsulation under the action of the serum in primary cultures as young as 2 hours or as old as 36 hours. The secondary growths did not show it. When the primary growth was injected into a mouse, the peritoneal wash also showed excellent capsulation with serum.

Findings. Sixty cases of lobar pneumonia were studied, 57 pneumococcic and 3 streptococcic. Of these, 54 (90%) yielded positive lung puncture cultures suitable for direct typing of the pneumococci by the Neufeld method and for cultural and morphologic recognition of the type streptococcus. It required 68 punctures in the 60 cases to obtain the aforementioned figures. Of the 60 initial or primary punctures, 49 (81.6%) gave positive cultures. Seven patients were punctured a second time, 4 yielding positive cultures; 3 punctures were done on only 1 patient, the third being positive. From the point of view of the number of punctures, 54 out of 68 (79.4%) were positive.

The lung puncture cultures were actually or practically pure in every instance. In 54 cultures only a single organism grew and this bacterium was unquestionably the causative factor in the infection. In 3 instances, after 48 hours, a contaminating white staphylococcus was also found but this was after the diagnostic work had been done and the subcultures made. In the first 48 hours all cultures were pure. A pneumococcus was recovered in 51 cases; a hemolytic streptococcus in 3. The pneumococci fell into the following types: Type 1, 12 cases; Type 2, 15 cases; Type 3, 3 cases; Type 4, 2 cases; and 1 case each of Types 5, 7, 8, 9, 14 and 18; 13 remained unclassified, lacking appropriate typing sera. The streptococcus cultures were easily identified by the marked hemolysis on the primary blood agar tube, making subcultures for further study unnecessary.

There would be no justification for doing lung puncture in lobar pneumonia with a view to serum therapy unless the organism could be recovered and typed within a short time. We endeavored to study this phase of the problem by examining the broth repeatedly at short intervals, though this was not always practical when the puncture and culture were made late in the day. In 33 of the positive punctures, the cultures were examined at 1 or 2-hour intervals

and the organisms found within 8 hours. At the end of 3 hours, 10 cultures were positive while at the end of 6 hours, the number increased to 29. Twenty-one punctures and cultures were made late in the afternoon and not examined until the next morning. The earliest positive culture fit for typing was in 2 hours; the latest, 36 hours. Thus, over half of the puncture cultures were positive within 6 hours and these figures almost surely would have been higher had frequent examinations in all cases been done. After the initial lag phase, the number of bacteria increased rapidly within a very short time. The first finding might show only 5 or 6 organisms in the whole spread examined rapidly; while an hour later, the same culture would show organisms in every oil-immersion field. Plotting the total number of positive cases for the time interval, the resulting curve (Chart I) simulates the accepted growth curve of bacteria.

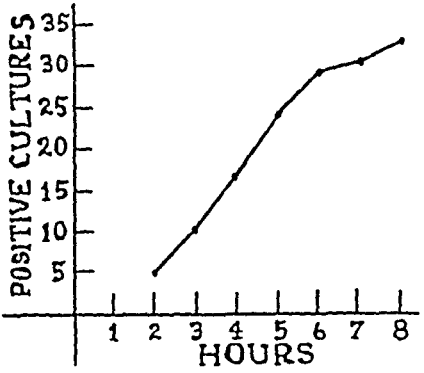


CHART I.—The number of cultures positive at the various hours after puncture.

The distribution of punctures with respect to the course or the day of the disease was fairly uniform. In the first 4 days of the disease 34 were done, 21 of these in the first 2 days; 29 from the fifth to the tenth day inclusive. In 5 cases, the day of the disease could not be fixed definitely. With the exception of the third day, when a comparatively small number of punctures were done, the percentage of positive cultures was consistently high during the first 6 days of the disease (Chart II). It may be noted that 10 punctures were made from the seventh to the tenth day inclusive. Of these, 7 were positive with 5 deaths; 3 were sterile with no deaths.

Sputum was present at some period of the disease in 57 cases. Of these, the sputum was present and typed at the time the lung puncture was done in 35 cases. It was satisfactory for direct Neufeld typing in 32 instances and by the mouse method in 3 instances. In 22 cases, the sputum was either absent or not obtainable up to the time the puncture was made. In 9 of these the sputum was later obtained and typed. A few cases had no sputum at any time. In 44 cases in which typing was attempted, the exact type was

determined in 25. In the remainder, typing was unsuccessful for want of appropriate antiserums. In the 25 classified sputa, the type ascertained was the same as that found in the corresponding lung puncture culture. In 24 the agreement was determined on the first typing. In 1 case only, a Type 4 was not found on the first attempt as was expected from the Type 4 lung culture: on the second attempt, however, Type 4 was demonstrated in the sputum.

The 3 streptococcus pneumonias were lobar in distribution and hemolytic in type and lung punctures were positive in all cases. The hemolytic type made recognition easy.

Blood cultures were done in 17 cases, 5 of which proved positive, 1 of these being a streptococcus hemolyticus, the others pneumo-

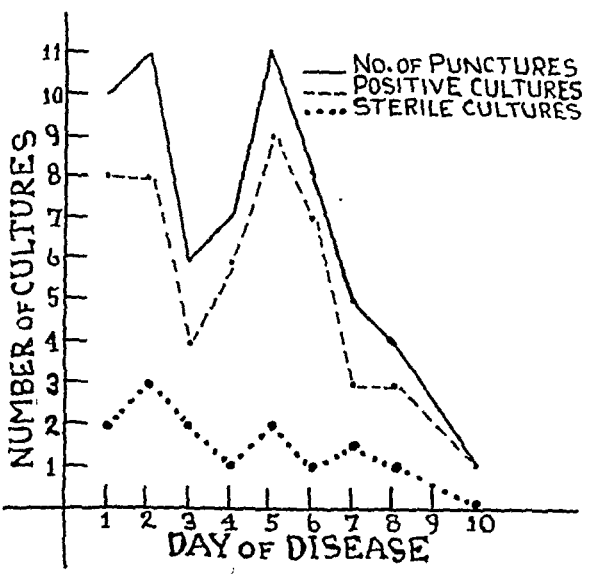


CHART II.—The correlation of 63 lung punctures, 49 positive cultures, and 14 sterile cultures with the day of disease.

coccic. In the 4 pneumococcic positives the blood and lung types agreed.

The mortality for the entire series was 40%, 2 of the 3 streptococcus pneumonias dying. Autopsies were held in 10 cases, enabling us to examine the site of lung puncture. No trauma was demonstrated from the puncture and in most cases it was difficult or impossible to find the puncture site. In 1 case in which there had been some hemorrhage after puncture no blood was found in the lung or bronchi and there were no signs of injury.

Sequelæ. In the natural course of lobar pneumonia, empyema is regarded as the most important frequent complication and one that might theoretically be anticipated after lung puncture. The frequency of this complication varies, depending in part upon the type of the organism. In Cecil's[25] large series of pneumococcus

pneumonias, the incidence of empyema ranged from 3.5 to 6.8% in the various types and averaged 5.1% for all types in 1913 cases. In our series of 57 pneumococcus pneumonias, empyema occurred in 5.3% of cases. But if the incidence of empyema be based on the number of lung punctures, which would seem logical, the incidence in the pneumococcus pneumonias was but 4.6%. The types found in the pneumococcus cases were 1, 3 and 8, and these agreed with the lung puncture types. One of the 3 streptococcus pneumonias developed empyema.

Hemorrhage developed immediately following lung puncture in 3 cases. In 2 it was trivial and only consisted of little bloody sputum for a few hours after the puncture. In another case, the bloody expectoration continued for some days, though it was never large in amount. This patient died of very extensive multilobar pneumonia and autopsy, as cited, showed no trauma or collected visceral blood.

Pneumothorax developed in 1 case. This occurred in the early part of our investigation, the patient being punctured 3 times at one sitting and the needle moved about after entering. We attribute this accident to our own poor technique at that time, though undoubtedly pneumothorax occurs occasionally when the technique is not to be criticized. This patient was actually improved after this pneumothorax.

There were no cases of sudden death after puncture or death attributable in any way to the procedure.

Comment. This review and study indicate, we believe, that lung puncture is reasonably safe and useful. Out of about 2000 lung punctures collected, there was only 1 case of sudden death[14] and, as a matter of fact, in this case the chest was being tapped for suspected fluid and the lung punctured unintentionally. There is no instance in this large series, of death from hemorrhage or pneumothorax. It is true, of course, that sudden death may follow chest puncture and Russell,[26] in criticizing Horder's paper[5] on lung puncture in 1909 cited 11 deaths following chest tap. Horder[27] effectively replies to this and concludes that this contingency is the rarest of events. And in the last 25 years, and particularly lately, with improved technique and diagnostic skill, the danger of sudden death or serious hemorrhage seems to have almost disappeared so that the conclusion of many writers that the danger is "negligible" would appear justified. In furtherance of this we would urge strict adherence to the technique cited, especially the use of small needles.

The usefulness of the procedure is seen in fact that 90% of 60 puncture cases yielded positive cultures which were pure and immediately adapted to Neufeld typing in the case of pneumococci. Half of the positive cultures were positive within 6 hours thus permitting early typing and therapy. We were able to type 38 of the positive

lung cultures as against 25 of the sputum organisms. Had all of the 32 pneumococcic antisera been available, these figures would of course have been increased for both. The advantage of lung culture typing is seen in the fact that in 22 of our cases the sputum was absent or not obtainable up to the time the puncture was made. Prognostic data in our small series were insufficient but what there are agree with those of Rosenow[7], and Thomas and Parker[14] in indicating that the viable lung organisms disappear in the later days in favorable cases and persists to death in unfavorable ones.

The 100% type agreement of the organisms of the sputum with those of the lung puncture cultures shows the reliability of the sputum in this respect. Therefore, in cases where the sputum is available and typable, lung puncture is unnecessary.

The technique herein detailed, the use of a single tube of blood agar with 1.5 cc. of plain broth at the bottom of the tube, is so simple and adequate that it is to be recommended. The very rapid growth of the lung organisms in this small amount of broth plus the few drops of lung blood or exudate allows early typing of the pneumococcus and usually the recognition of the type streptococcus.

Four of the lung punctures were done after antipneumococcus serum had been administered: all 4 of these gave positive cultures. Two Type 1 cases gave positive cultures 3 and 24 hours respectively after 20,000 units of serum. A Type 2 case was positive 3 hours after 10,000 units of serum: and another Type 2 case gave a positive culture 24 hours after 20,000 units. Three recovered; 1 Type 2 case died.

One patient gave a Type 2 pneumococcus in the sputum and from the lung. Reference to a hospital admission 8 months previous, showed he then had Type 2 pneumonia. He recovered.

Summary. With a simple and apparently safe technique, 60 cases of lobar pneumonia (57 pneumococcic and 3 streptococcic), were subjected to diagnostic lung puncture. Positive cultures, suitable for typing, were obtained in 90%, half of these within 6 hours. Lung puncture cultures made 3 and 24 hours after the administration of antipneumococcus serum were positive. In 25 cases in which both the lung and sputum pneumococcus were typed, there was 100% agreement. Where sputum is at once available, therefore, lung puncture is unnecessary. In 22 of the cases, however, the sputum was either absent or unobtainable at the time the lung puncture was made. The method is, therefore, recommended for early diagnosis and typing when sputum is not as quickly available.

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THE ASSOCIATION OF ERYTHREMIA AND DUODENAL ULCER.

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In August, 1932, Morris[1] *et al.* inferred from their findings in the blood in erythremia that the disease was due to an overproduction of the blood-forming hormone, which they named "addisin." They propounded the theory that erythremia was due either to excessive secretion of "addisin" by the stomach or due to an increase in the susceptibility of the bone marrow to stimulation by "addisin." They suggested that erythremia be treated by lessening the gastric secretion. A year later the Morris group[2] definitely concluded that "addisin," the hemopoietic factor secreted in the normal stomach, was identical with the "intrinsic factor" of Castle.[3] They treated

a case of erythremia by lavaging the stomach 3 to 4 times weekly in an attempt to diminish the body's supply of "addisin." In the course of 6 months their patient's blood count fell from 10 to 5.3 millions. A few months after the lavage was discontinued the count had again risen to 10.2 millions.

Their patient had a duodenal ulcer associated with the erythremia. This association of erythremia and duodenal ulcer seems to be more than coincidental. The subject of the association of these two diseases has recently been discussed by Boyd,[4] who, after reviewing the literature and reporting a case, reached the conclusion that polycythemia bore a causal relationship to duodenal ulceration.

Wilbur and Ochsner[5] have also abstracted the literature regarding the concurrence of these diseases and have carefully investigated 143 case records of erythremia at the Mayo Clinic. In 8% of their cases there was roentgenologic evidence of gastric or duodenal ulceration. In a control series of 200 cases of hypertension the incidence of ulcer was only 2%.

We have recently observed 2 patients having erythremia and duodenal ulcer associated. Both patients were Russian Jews employed in tailoring establishments. The gastro-intestinal complaint was predominant in both cases. The first case presents nothing of unusual interest, and it is offered merely because it adds another case to those already reported of the association of these two diseases.

Case Reports. CASE 1. S. B., a white male, aged 52, complained of pain at the ensiform cartilage after meals. The pain was relieved by food. This symptom had persisted for 2 years, and the patient had had no illness of significance previously. The skin of the face was purplish-red and the mucous membrane of the mouth was deep red. There was marked epigastric tenderness. The red blood cells numbered 9,400,000 and the hemoglobin was 140%. Roentgen rays taken elsewhere showed a duodenal ulcer. The patient refused to permit extensive study of his case as he was interested only in relief from the ulcer symptoms and could not be persuaded of the significance of his blood dyscrasia. He was given an alkalin powder and a hyperacidity diet and was not heard from again.

The second patient was more coöperative. We attempted a series of lavages, not only to relieve the ulcer symptoms but also in the hope that the erythremia might improve as it did in the case treated by Morris and his associates.

CASE 2.—J. F., a white male, aged 49, came to us on November 21, 1933, for relief of "stomach trouble." He complained of epigastric pain and sour water brash. The symptoms appeared about 3 hours after meals and were relieved by food. These complaints had their onset in January, 1933. He sought medical advice in the summer of 1933, and was told that he had an "acid stomach" and was treated unsuccessfully with diet and alkalis by two successive physicians.

In addition to this gastro-intestinal history, he informed us that he was a sufferer from polycythemia vera. He had become aware of this blood dyscrasia early in 1932. At that time a sebaceous cyst was removed

from the back of his neck at a physician's office. The bleeding was so severe that to control it the patient was removed to a hospital. There the diagnosis of erythremia was made. From June, 1932, until February, 1933, he was treated for the erythremia at the Stuyvesant Square Hospital Clinic of New York. This clinic was kind enough to supply us with information about the patient. He had been given phenylhydrazin in capsules. The red cells fell from 9 to 6 million, but returned again to 9 million after the drug was withdrawn in February, 1933.

Physical examination: Blood pressure, 150/100. Skin of face and hands was of a purplish hue. Mucous membrane of the mouth and pharynx was deep red to purple in color. The heart, lungs, abdomen and reflexes showed no abnormalities. However, a Roentgen ray film of the chest showed considerable increase in bronchial and vessel markings.

Laboratory examination: The urine contained a large quantity of albumin and many granular casts. The red blood cells numbered 8,750,000; hemoglobin, 135%. Fractional gastric analysis showed a curve of hyperacidity, continuing high over most of the test period of 2 hours. Occult blood was present in all specimens. Gastro-intestinal fluoroscopy and Roentgen-ray films disclosed the typical deformity of duodenal ulcer.

Diagnosis: Duodenal ulcer. Erythremia. Chronic nephritis.

Course: Knowing that gastric lavage would greatly relieve the ulcer symptoms, and in view of the benefits obtained by Morris in erythremia, we employed this treatment in our case. We prescribed a bland diet and alkalis and instituted biweekly lavages, which were carried out over a period of 3 months. The patient arrived at the office for his lavage about an hour after a breakfast of a cup of coffee. The stomach was washed 10 times at each visit with 300-cc. portions of dilute bicarbonate of soda solution, administered and withdrawn through a narrow Rehfuss tube. After a few weeks, occult blood was absent from the return wash water, and after 2 months the symptoms of ulcer disappeared. The red blood counts taken from time to time were as follows:

November 21, 1933: 8,750,000; hemoglobin, 135%.
December 8: 9,000,000; hemoglobin, 138%.
January 9, 1934: 9,070,000; hemoglobin, 144%.
February 23: 9,500,000; hemoglobin, 130%.

When the patient was cured of his painful ulcer symptoms, and since he knew that his red blood cells were not being reduced, he was no longer content to continue the lavages. In March, 1934, treatment was discontinued. A follow-up in May, 1934, revealed that the patient was still free from his ulcer symptoms and was receiving Roentgen ray therapy for his erythremia.

Comment. Apparently not all cases of erythremia are benefited by lavaging "addisin" from the stomach. It is possible that we did not carry out frequent enough washings. Oerting and Briggs[6] lavaged their patients 4 to 6 times daily, and thus obtained a reduction in the red blood cells. The difficulty of persuading a symptom-free patient to consent to such a procedure can readily be realized. However, it is only by trying this treatment on all cases of erythremia that its values can be determined. Lavage of the stomach affords such great relief to ulcer sufferers that they are willing to continue the treatment for long periods of time.

Should a patient with erythremia and duodenal ulcer associated show a marked reduction in erythrocyte count after gastric lavage, gastrectomy might afford permanent cure of both afflictions. This

operation would remove the source of "addisin" and at the same time cure the ulcer. At least, it is interesting to speculate on curing erythremia by gastric resection.

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AMEBIASIS AND CANCER OF COLON.

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In his *Clinical Medicine*, Trousseau[1] says, "I repeat that dysentery is the most formidable and dangerous of all epidemic diseases. Even when patients have resisted its first assaults, and seem to be reaching convalescence, danger is not past, and there are evil consequences to be dreaded after the disease." Trousseau's characterization included amebic dysentery and seems to have particular force when we consider so serious a sequel of it as cancer of the large bowel.

Attention has been called frequently to amebic lesions of the colon which were mistaken for carcinoma. Cancer has been mentioned by various writers as a possible sequel of amebic dysentery. Remarkably little has been reported on the association of cancer with amebic dysentery, and the masking of malignant symptoms by indications of amebiasis.

The first half of the picture, amebic lesions simulating cancer, has been presented, among others by Desjardins,[2] who states that undoubtedly operations are performed under this wrong diagnosis. He calls attention to masses consisting of a true neoplasm of amebic origin, or an inflammatory mass secondary to an amebic ulcer, or to

an amebic ulcer alone. He describes a characteristic patient, aged 40 to 50 years, with persistent attacks of pain in the right lower quadrant, difficulty in defecation, alternating constipation and diarrhea, with mucoid movements at times bloody. Examination shows a hard irregular mass either fixed or movable with the colon. The Roentgen ray may show a filiform narrowing. The whole picture seems one of cancer but the mass is made up of spastic bowel and inflammatory products of an ulcer.

Gunn and Howard[3] report 3 cases of amebic granulomas simulating cancer. The pathology in these cases consisted of persisting, "isolated, chronic ulcer with progressive erosion of the wall of the bowel." Edematous fibrous granulation tissue was produced in large quantity resulting in definite tumor masses. These amebic granulomas may "give symptoms, physical signs, and radiologic appearances that may be identical with those produced by carcinoma." This important report deserves careful study. The authors comment on the rarity of reported amebic tumor formation, and could find only 6 authentic cases beside their own. They note that amebas may appear in the stools only occasionally, if the amebic colonization is limited to the tumor mass, thus making preoperative diagnosis even more difficult. Rogers[4] refers to 2 cases of supposed cancer, in which amebas were found, and which were cleared up by emetin treatment. The present writers have seen 3 cases in which definite tumor masses were found in the colon but in none was the mass isolated, arising from a single ulcer as described by Gunn and Howard. Extension of the lesion to various parts of the colon is strongly against a diagnosis of cancer. Amebic tumors tend to disappear with medical treatment but their failure to do so does not rule out an amebic lesion. Gunn and Howard observed coexistence of amebiasis and cancer, and note that Roentgen ray findings may not distinguish between the two.

A case of polyposis of the colon has been described by Hines[5] in which "the colon mucosa presented no gross signs of ulceration, but was the site of multiple confluent polypoid masses." Hines describes the frequent formation of polypoid masses at the margins of healing dysenteric lesions. He quotes Kaufmann[6] who noted their presence in tuberculous ulcers of the colon, and refers to descriptions of their occurrence in amebic lesions. Here we have a possible method for the development of cancer from an amebic lesion, through the transitional stage of polyps or small adenomas.

Cancer of Colon and Rectum. Carcinoma of the colon is nearly always primary. Rarely it has been reported as secondary to a tumor higher in the intestine, when direct implantation and not metastasis is probably the explanation. Rarely, also, multiple growths in the colon have been reported. In the colon carcinoma metastasizes late and slowly to the liver and lymphatics, and tends to remain localized for a long time. Metastasis elsewhere is uncom-

mon, but may occur as shown in Case 3 below. Cases have been reported from early childhood to extreme old age. In general, rectal cancer tends to appear at a later age. In the colon, spread is by contiguity and by extension of an intrinsic tumor which thus tends to cause obstruction. Obstruction is rarely or never complete but commonly results in proximal dilatation and hypertrophy of the bowel and may cause intussusception or angulation. The rate of growth is characteristically slow. The favored site is in the sigmoid, and descending colon, followed by the ileocecal region and cecum, and then the hepatic and splenic flexures.

In the rectum, Tuttle[7] placed 67% at the rectosigmoid junction, 26.3% in the ampulla and 6.7% in the anus. Epithelioma can occur only at the anal skin edge and only an involvement of skin tissue can lead to extension to the inguinal glands. Rectal growths tend to spread in all directions with circular extension common. Rectal cancer is some 8 times more common than colonic cancer. The great majority of cancers of the colon and rectum are adenocarcinomas, which tend to metastasize less rapidly than other forms. Scirrhous carcinoma and lymphosarcoma are uncommon. Lymphosarcoma is amenable to Roentgen ray treatment and Roentgen ray examination after a 2 weeks' interval will show definite regression.

Clark,[8] in reviewing the distribution and complications of amebic lesions in 186 postmortem examinations performed by him, reports the following: "About 60% of the series possessed ulcers more or less all through the colon, while 40% had a local distribution in the more dependent parts of the colon and appendix. The local incidence for age and number of lesions can be placed in the following order of importance: the cecum and ascending colon, the rectum and sigmoid, and the appendix. The results are in conformity, more or less with the report of Kartulis except in regard to the appendix." Clark states elsewhere that but 27 of the 186 cases had a known history of one or more previous attacks of amebiasis and these patients were under treatment for the disease. This shows a striking similarity in the sites of election in amebiasis and in cancer of the large bowel.

Cancer is prone to follow simple tumors such as polyps and adenomas of the colon and to develop at points of long-continued irritation. Such points are afforded by long-standing ulcers, fistulas and constrictions. Chronic amebiasis affords an excellent background, therefore, and cancer must be considered as a possible sequel. The exciting cause of the change from chronic benign process to rapid malignant process is unknown and no method is available for diagnosing the imminence or the occurrence of this transition. Altered sedimentation rate and other blood changes are not helpful because of the close masking intermixture of secondary bacteria with the entire process, both in its benign and in its malignant phases. Also, the response to bacterial invasion overshadows the

body reaction to malignancy so far as the sedimentation rate is concerned. Cure of colonic and rectal cancer is exactly proportioned to earliness of diagnosis, permitting surgical removal in an operable stage, or Roentgen ray treatment in the case of lymphosarcoma. Obstructive symptoms usually, but not always, indicate inoperability (see Case 1 below). The patient's future thus depends on his early consultation with the physician, when any part of the symptom-picture noted below arises, and very definitely depends on consideration, by the consultant, of the possibility of cancer. Furthermore, when cancer can be proved absent, care must be exercised to remove accessible benign growths, to correct so far as possible mechanical defects and to cure as quickly as possible specific dysenteries and amebiasis. The advisability of colon resection as a preventive measure must be considered in cases of polyposis especially where the favored cancer areas are concerned.

The symptoms of cancer of the colon may be summarized as follows:

1. *Pain.* This may be merely a sense of discomfort and vague unrest with undue consciousness of the abdomen. Frank pain is extremely variable, may be absent until late, but, in our experience, is usually fairly early and decidedly significant. It tends to be localized although not necessarily in the region or zone of the lesion. It may be in the sacrum or anywhere in the abdomen. It may be of a burning character, intermittent or constant, or periodic. It may be associated with difficulty in securing free evacuation of the bowels. It may be due entirely to partial obstruction, which, in the descending colon and sigmoid, may disappear completely, not to recur even for several months. Obstructive pain may appear suddenly and acutely, with nausea and vomiting and the general picture of acute obstruction.

2. *Diarrhea* is a common early symptom and, if repeated within an interval of a few months, or, if persistent or chronic, should have an intensive study to eliminate cancer of the large intestine. Mild diarrhea on first rising in the morning should be a cause for suspicion.

3. *Constipation* and *obstipation* arising anew must receive similar consideration.

4. *Mucus* and *blood* in the stools invariably must receive an adequate explanation. If attended by painful and too frequent bowel movements, they constitute dysentery. If a specific cause, as, for instance, *Endamœba histolytica*, *Balantidium coli* or *Bacillus dysenteriæ*, is found and properly treated with no relief or only temporary relief of symptoms, further studies, including Roentgen ray, especially after barium enema, should be instituted promptly, and cancer should be diagnosed or consciously excluded.

5. *Tumor* may be the first sign, especially in the cecal region.

6. *Constitutional symptoms* of anemia, asthenia and loss of weight usually develop slowly, but in the 4 cases here reported, loss of weight was among the earliest symptoms noted.

7. *Persistent indigestion or changed bowel habit* in a person previously free of symptoms should excite suspicion.

In general, obstruction is usually seen in the annular, more scirrhous type of cancer in the descending colon and sigmoid, while toxic and constitutional symptoms are prone to attend cecal cancer.

Special Diagnostic Procedures. (In order of importance.) 1, Sigmoidoscopic examination should invariably be made but will not always be helpful, especially with cancer at or above the sigmoid flexure. If scirrhous cancer is present, there may be little or no change in the mucous membrane of the colon. Resistance to passage of the sigmoidoscope may be noted at or above 15 cm.

2. Barium enema and Roentgen ray examination localize the tumor and show the extent of involvement. It is most important to have the patient empty the bowel of barium and retake the Roentgen ray as an aid in early diagnosis.

3. Gross and microscopic fecal examination, for cellular, bacterial, chemical and food elements. Exhaustive search for protozoa is imperative.

4. Biopsy and study of histologic sections of masses found on sigmoidoscopic examination.

Case Reports. CASE 1.—(April 4, 1934.) Mrs. G. L. H., aged 49, widow, for 15 years has traveled constantly in South America, Asia and the Far East. Her previous history was not significant. The *present illness* began in 1924 as generalized abdominal pain, flatulence and bloating. In 1926 the condition was finally authoritatively diagnosed as amebiasis. At that time she received emetin and chiniofon. She has had frequent recurrences and exacerbations up to now. The stools showed blood, mucus and pus most of the time. During exacerbations she was treated and relieved repeatedly by emetin and chiniofon. One year ago, the picture gradually changed with an increased severity and localization of the pains in the upper left abdomen. Dysentery continued. Amebas were found no more. Relief did not follow the use of emetin and chiniofon. The patient lost 18.1 kilos in weight, and felt herself losing in strength and general vigor. Six weeks ago anemia was noted for the first time. Three months ago while in the Orient she suffered an attack which was probably due to partial obstruction of the colon.

Examination showed considerable pallor and evidence of wasting. There was tenderness under both costal margins, with no visceral enlargements. Varices of the legs were apparently of many years' duration. The blood pressure was a low normal and the pulse rate increased, results of anemia, weakness, and probably long use of emetin.

Laboratory Results. Urine, normal. *Blood count:* red cells 3,000,000; hgb. 9.7 gm.; white cells 18,920, with 79% neutrophils, 15% lymphocytes; 4% monocytes; and 2% eosinophils. *Stools* showed cysts of *Endolimax nana* and active trichomonads. Exhaustive search failed to reveal *E. histolytica. Stool culture* showed no growth of non-lactose fermenters of either the typhoid or dysentery groups. *Blood Wassermann* and *Kahn* tests were

negative. *Blood agglutinations* were negative for *B. dysenteriæ* of all types, typhoid and paratyphoids, brucella, and *B. enteritidis*. *Blood sugar* was 123 mg.; blood calcium 10.1 mg. per 100 cc.

Roentgen ray examination with barium enema showed an initial spasticity of the upper sigmoid region which later filled out normally. The rising barium column met with a fixed irregularity in the splenic flexure at a point corresponding with the painful point noted by the patient. Barium passed through this narrow ragged region, causing the patient considerable distress. The proximal colon had a normal appearance. The Roentgen ray conclusion was that the appearance favored neoplasm, but did not exclude an intrinsic lesion or granuloma of the bowel wall.

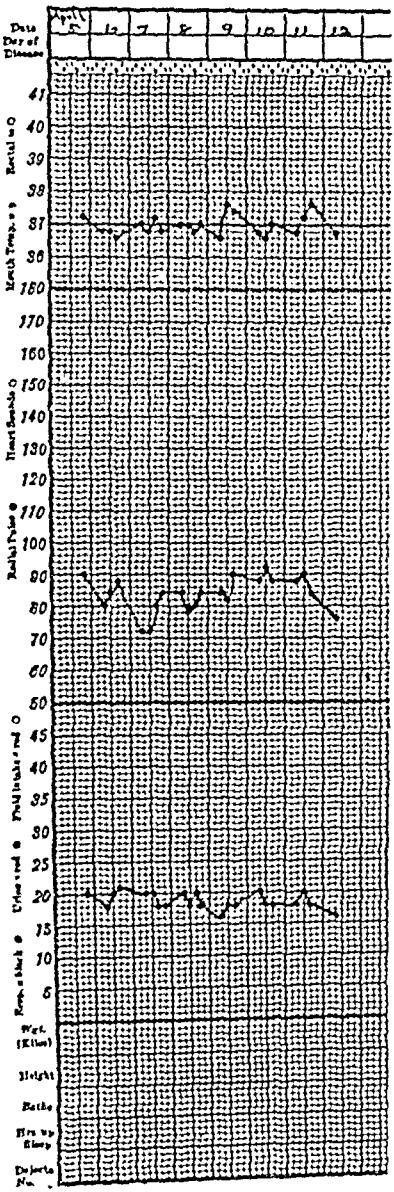


FIG. 1.—Case 1. Pre-operative chart.

Temperature, pulse and respiration are seen on accompanying chart.

Diagnosis. 1, Lesion of splenic flexure, probably carcinoma, possibly amebic granuloma; 2, secondary anemia and malnutrition; 3, history of about 9 years of amebic colitis, ending within the past year.

Subsequent Course. The patient was given 1 grain (0.065 gm.) of emetin hydrochlorid hypodermically daily for a total of 5 grains (0.33 gm.). This was followed by chiniofon which, however, caused serious colic and diarrhea, and was stopped after 10 doses. Vioform (0.5 gm. twice daily by mouth) was given to a total of 20 doses. It was felt that any amebic lesions would be controlled at least by this procedure, that a change in the Roentgen ray findings would be an indication of an amebic lesion rather than of malignancy, and that the risk of laparotomy would be reduced by removal of the whole or a large part of the amebic hazard. The pain decreased. The patient showed much weakness, with a pulse of 90 and blood pressure of 110/70. There was no significant change in the blood count. After the termination of the anti-amebic treatment noted the barium enema was repeated 3 weeks subsequent to the first Roentgen ray examination. The conclusion was that the same lesion was present unchanged. A definite diagnosis of carcinoma of the splenic flexure was made at this time.

One week later laparotomy (Dr. H. Glenn Bell) revealed a tumor of the splenic flexure with no evidence of metastasis. The left lobe of the liver was greatly enlarged and hepatic adhesions were found, indicating old

extensive hepatitis. The spleen was very small. The colonic mass was 6 by 5 cm. in area, involved the wall of the colon and was characteristic of carcinoma. A lateral colon anastomosis was done, short-circuiting but not closing off the splenic flexure and tumor. The patient went through a stormy convalescence protracted by a wound infection, and pneumonia of the left lower lobe. She finally left the hospital in fairly good condition, 52 days after the operation.

She was readmitted 15 days later for the second laparotomy and resection. Her blood count was now hgb., 5.2 gm.; 2,520,000 red cells; 11,600 white cells with 73% neutrophils. The urine was normal. After transfusion, the tumor was resected by Dr. Bell. The hemoglobin dropped to 3.4 gm., 5 transfusions followed, and a fecal fistula developed which closed after about 2 months. The tumor was removed by cautery. Again no evidence of metastasis could be found. The bowel was closed by end-to-end anastomosis. Convalescence was protracted and eventful, the patient finally being discharged in good clinical condition. She remained well for 9 months following removal of the tumor. The pathologic diagnosis of the tumor by Dr. James F. Rinehart was adenocarcinoma of the large intestine. A thorough check-up 5½ months after operation showed normal stool analysis with no amebas or other parasites except trichomonads. The blood count was hgb. 13.1 gm. and 3,840,000 red cells. The patient died suddenly 10 months after operation from an apparent recurrence of the carcinoma at the splenic flexure, though autopsy was not obtained.

CASE 2.—E. F. B., aged 49, widower, when first seen on March 10, 1933, complained of blood in the stools for 1½ years past. He had lost 52 pounds in that time. Bowels moved 3 to 4 times daily. Nausea and vomiting were absent. Looseness of the bowels had been noticed for some 4 years, with increasing pain and colic. His other complaints were increasing weakness and nervousness.

His previous medical history was limited to excessive use of tobacco and considerable recurring dental infection. He was born in Nebraska, was never outside the U. S. A., and had lived in San Francisco for the past 32 years.

Examination showed a pale, lethargic man with evidence of wasting. The blood pressure was 90/58, with a pulse rate of 80. The abdomen was relaxed. The sigmoid was cordlike and tender, and a boggy cecum could be felt. The liver was somewhat enlarged and tender.

Laboratory Findings. Urine was normal. Blood count showed 80% neutrophils, 31% lymphocytes, 3% mononuclears and 1% eosinophils; red cells 4,650,000. *Stools* exhibited much blood and mucus but no parasites were seen. Sigmoidoscopic examination showed a normal mucosa with some gray mucus high up which contained abundant motile *E. histolytica.* Roentgen ray examination by barium enema was reported by Dr. I. S. Ingber as follows: "The colon fills normally. There is no evidence of an organic lesion."

Diagnosis. Amebic colitis, with possible amebic hepatitis. Hypotension.

Treatment consisted of 8 courses (5 gm. each) of carbarsone by mouth, 1 course rectally, and 3 courses (5 gm. each) of vioform over a duration of 9 months. There was excellent clinical improvement with a weight gain to 168 pounds. After cessation of treatment, amebas were not found on repeated examinations and the patient was able to return to hard work.

On August 7, 1934, 8 months after termination of treatment, he complained of occasional colic and blood in the stools. No amebas were found. He was relieved of the colic by omitting coffee and tea. After 2 weeks, abdominal pain became severe, especially in the hypogastrium and on the left side. The abdomen was excessively tender and a hard mass was pal-

pable deep in the lower left quadrant, apparently arising in the sigmoid. Sigmoidoscopic examination was negative. Barium enema Roentgen ray showed an obstruction in the lower sigmoid, allowing filling only of the rectal ampulla. The pre-operative diagnosis was abscess, amebic granuloma, or new growth.

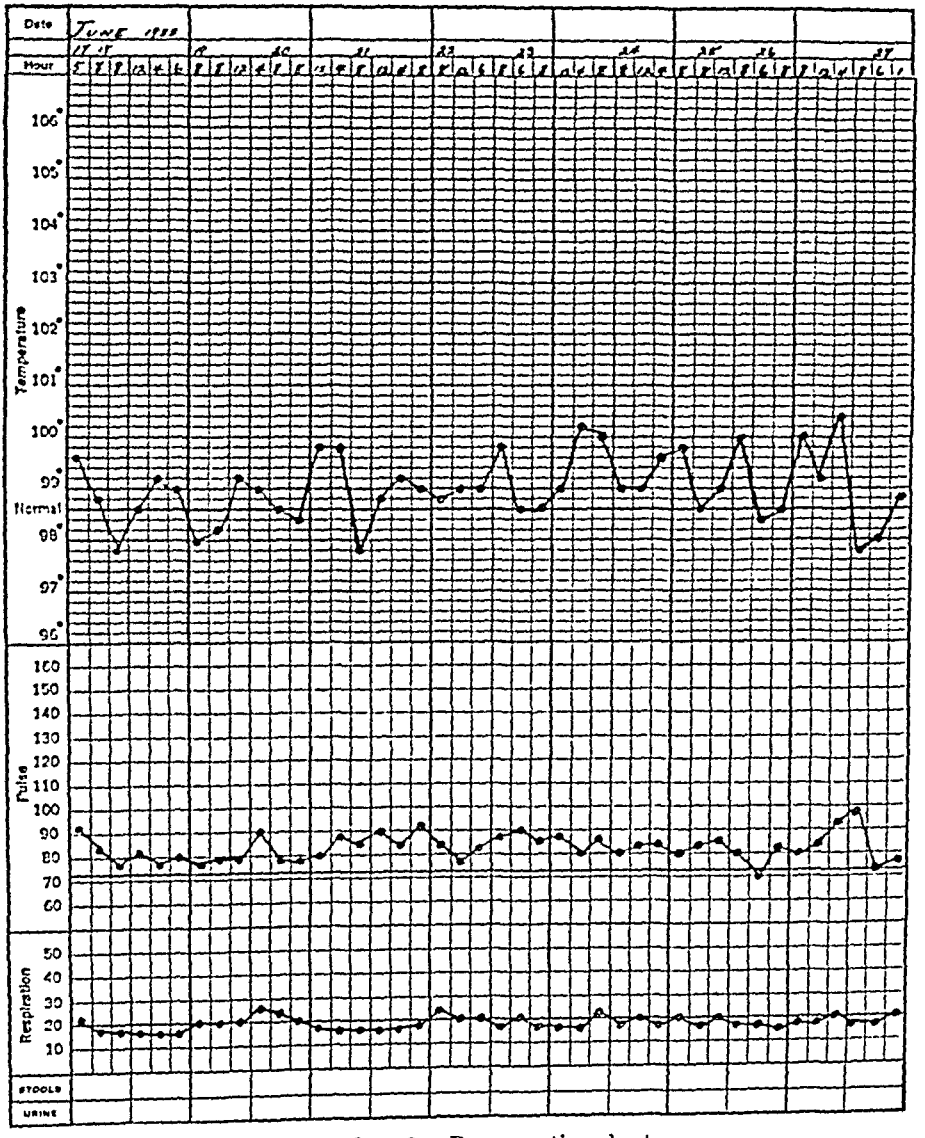


FIG. 2.—Case 2. Pre-operative chart.

Laparotomy was performed by Dr. Dudley Smith who found a mass the size of a large orange involving the sigmoid colon, fixed, hard and inseparable. Cecostomy and colostomy were done. Postoperative diagnosis was cancer of the sigmoid, inoperable. Ten months after operation, the patient was still relieved of obstructive symptoms but his general condition was failing.

CASE 3.—J. B. F., male, aged 40, was first seen February 4, 1935. *Present illness* began 7 years ago in Los Angeles as a diarrhea with occasional blood in the stools. There was no pain and no fever. *Endamœbæ histolyticæ* were found and have been present at various times up to 1 month ago in spite of treatment. Therapy has been varied and nearly

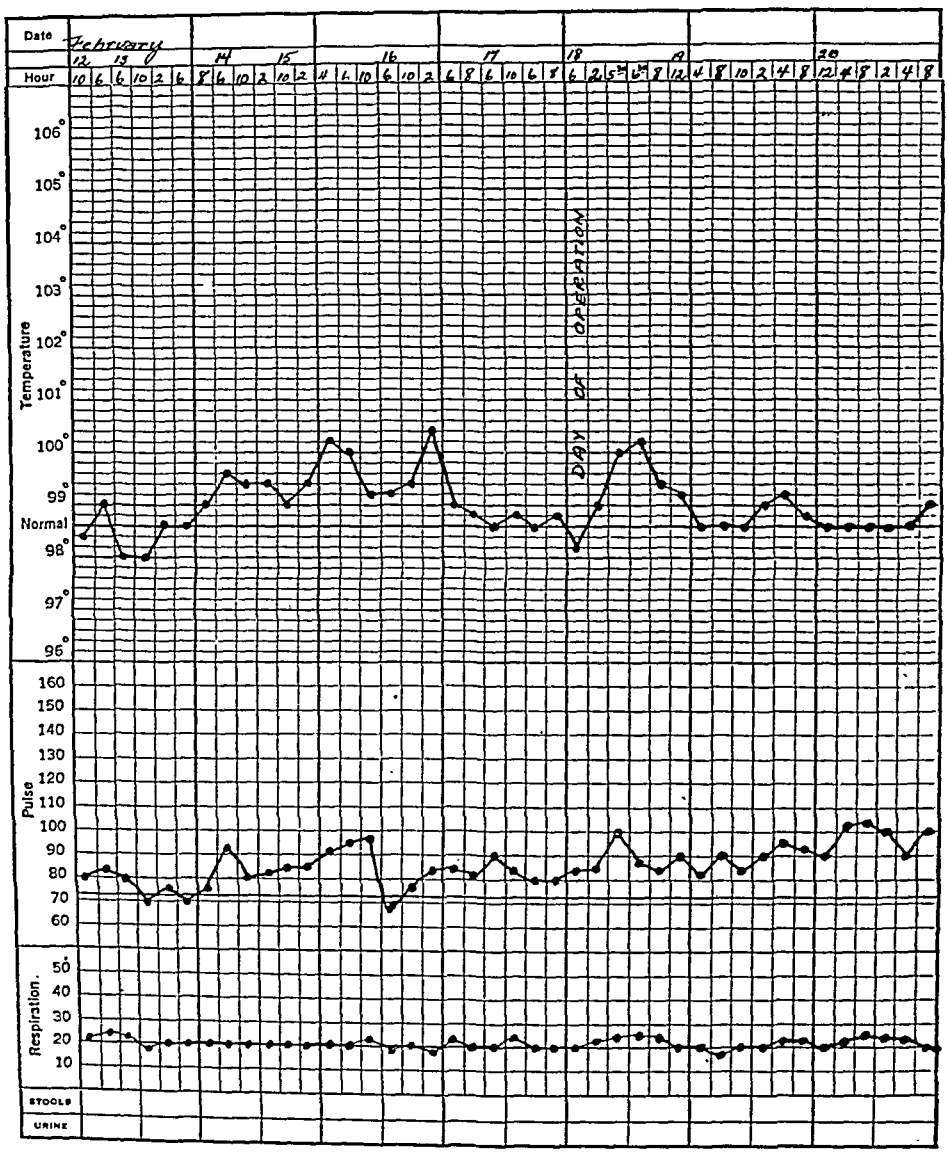


FIG. 3.—Case 3. Pre-operative chart.

constant, including a gall-bladder drainage, emetin courses, acetarsone over a period of 2 years, chiniofon, autogenous vaccines, tannalbin, and finally carbarsone. He has noted an intolerance for carbohydrates which cause diarrhea with foamy stools. Symptomatic temporary relief always follows administration of carbarsone. Barium enema Roentgen rays by Dr. L. T. Stephens, Seattle, November 16, 1932, gave the following conclusions:

"Barium enters rectum normally, which is small and does not dilate. Barium passes up rapidly through a tortuous narrow descending colon with complete absence of haustration. In the middle half of the descending colon on external surface are a number of small protuberances. On the opposite side over midportion of ileum is a much larger protuberance. These protuberances suggest ulcers. Barium passes rapidly across transverse colon, rapidly into cecum and small bowel. Lower bowel is remarkable for absence of haustration. No constricting bands were visualized in region of ileum or cecum. Conclusion: Spastic ulcerated colon."

Past History. The patient's father died with chronic arthritis at 61 years, and one brother now has chronic arthritis.

The patient was born in Manitoba, and since the age of 3 has lived on the Pacific Coast of the United States, with trips to New Orleans and Tia Juana. He had all the usual childhood diseases, and diphtheria at 15 with a history of cardiac involvement. When taking emetin, he has noticed mental slowing and weakness and pains in the lower extremities. Lately he has noticed dyspnea on exertion, pronounced weakness and had a fainting spell 1 week ago. He is abstemious in diet and habits, uses no alcohol or tobacco, and cannot take coffee because of its laxative effects. His weight has dropped from a normal of 150 pounds to 136 pounds.

Examination showed moderate pallor, evident weakness and poor muscle tone. The heart was not enlarged, blood pressure 110/70 (Tycos) with no murmur but a tendency to increased rate (80 to 88).

Laboratory Findings. Urine, normal. *Blood count,* moderate secondary anemia only. *Stools,* no amebas on repeated search. A few Charcot-Leyden crystals, many red blood cells, moderate mucus, many short-chained streptococci. *Blood Wassermann* and *Kahn* tests were negative. Blood calcium, 8 mg. per 100 cc.

Electrocardiogram. Rate 63. Normal rhythm. Slightly slurred R in II and III, and of S in II and III. *S–T* interval elevated in III. Suggests myocardial damage.

Roentgen ray examination of the *abdomen* by Dr. R. F. Kile gave the following summary: The colon is fairly well outlined, possibly due to previous medication, such as bismuth powders. No abnormality or distention of the bowel is noted. The liver is not enlarged and there is no evidence of a subdiaphragmatic abscess. The right kidney shadow is well defined and the psoas shadow is normal, which would rule out the possibility of an abscess about the kidney.

Barium enema shows a marked constricted area at the rectosigmoid junction which is approximately 4 inches in extent. The channel through this portion of the bowel is less than a cm. in diameter. Throughout the entire descending, transverse, ascending, cecum and terminal ileum, there is marked irregular filling with many areas suggesting ulceration.

Conclusions. Ulcerative colitis, which involves the entire colon and terminal ileum, constricting an area of sigmoid, suggesting an inflammatory mass.

Diagnosis. Amebic colitis beginning 7 years previously, and eventually cured. Carcinoma of sigmoid with partial obstruction and probable metastases.

Operation (Dr. I. W. Thorne, February 18) revealed an inoperable carcinoma of the sigmoid, with metastases in the mesentery of the small intestine. A permanent cecostomy was done. Death ensued on March 31, 1935.

Necropsy (Dr. Z. E. Bolin). *Anatomic Diagnoses.* 1, Adenocarcinoma arising in the sigmoid colon with extension to the sigmoid mesentery, retroperitoneal lymph nodes, first, third and fourth lumbar vertebræ; with

metastases to the peritoneum, diaphragm, both pleural cavities, pleura of both lungs, liver, gall bladder and pericardium; 2, bilateral pleural effusion, carcinomatous in origin, right 200, left 500; 3, pericardial effusion 100 cc.; 4, marked emaciation; 5, dilatation of the heart with brown atrophy; 6, chronic passive congestion of the viscera; 7, abscess right parietal region extending from the base of the skull to the clavicle, staphylococci and B. coli in origin; 8, cecostomy opening; 9, acute splenic tumor; 10, edema of lungs, slight; 11, generalized arteriosclerosis.

CASE 4.—B. A. B., male, aged 48, was first seen April 3, 1933, complaining of loose bowel movements with blood in stools and loss of 23 pounds in weight during past year. The symptoms began with diarrhea and bleeding external hemorrhoids 3 years ago. For 2 years these were only symptoms. During the past year, blood has been increasingly frequent in the stools, associated with much mucus and at times some colic. He has been passing about 10 to 14 loose stools each day. The hemorrhoids had disappeared. Lately he has had pain under and above the right costal margin.

His mother died at 72 years of a stomach tumor. He was born in Nebraska and always lived in the States between Nebraska and Northern California. He was a rancher until 12 years ago when he became a high school teacher. For years he had worn a truss over a right inguinal hernia. In 1921, "flu" with hemoptysis led to suspicion of phthisis which was never confirmed. He had had pleurisy at one time.

Examination showed a thin abdomen with palpable, hard, tender sigmoid and descending colon. The cecum was thickened and hard. The liver edge was 4 finger breadths below the costal edge, smooth, and tender in the region of the gall bladder. There was no jaundice. The only other abnormal finding was inequality of the pupils. Sigmoidoscopic examination to a depth of 22 cm. showed an intensely congested mucosa with a few superficial ulcers high in the rectal ampulla. There was much adherent gray mucus.

Laboratory Findings. Urine, normal. *Wassermann* and *Kahn* tests, negative. *Phenolsulphonphthalein* excretion, 35% in 2 hours. *Blood count:* Red cells 3,520,000; hgb. 13.2 gm.; white cells 6920; neutrophils 64%, lymphocytes 27%, mononuclears 4%, eosinophils 2% and basophils 3%. *Stools* showed motile *E. histolytica* with much blood and mucus.

Diagnosis was made of amebiasis, hepatitis (possibly amebic), amebic colitis and secondary anemia.

Treatment for the amebiasis consisted of carbarsone (10 gm.) and vioform (7.5 gm.) for 1 month with dietary control, vitamin B and bismuth subcarbonate. Symptoms improved, the liver pain disappeared and he gained 8 pounds in weight. Amebas were not found again on repeated search. The liver retreated within 2 finger breadths of the costal edge.

Further Course. Improvement was temporary and in spite of the absence of amebas, diarrhea easily recurred, at times with some blood. In an effort to insure that amebiasis was not responsible further for the condition, emetin hydrochlorid was given hypodermically; 1 grain (0.065 gm.) daily for 5 days. No change in symptoms followed. Roentgen ray of the colon with barium enema on April 27 showed marked spasm of the lower descending colon and sigmoid which was reported as irregular in character and having the characteristics of inflammatory induration rather than of neoplasm.

Examination showed apparent improvement in the abdominal condition. The colon was not palpable nor tender. The liver descended 2 finger breadths only, was smooth, firm and not tender. No jaundice was present. There was some edema of the legs. Symptomatic colonic treatment with bed rest gave clinical improvement. On May 29, abdominal pain, nausea and watery diarrhea appeared, followed by sudden severe pain over the

liver area. The white cell count rose to 15,520. There was no fever. Roentgen ray studies showed normal lung fields and heart contour, with a limited mobility of right diaphragm and marked enlargement of liver. There was no definite evidence of liver abscess. Improvement again took place. On recurrence of symptoms 2 weeks later, gastro-intestinal Roentgen

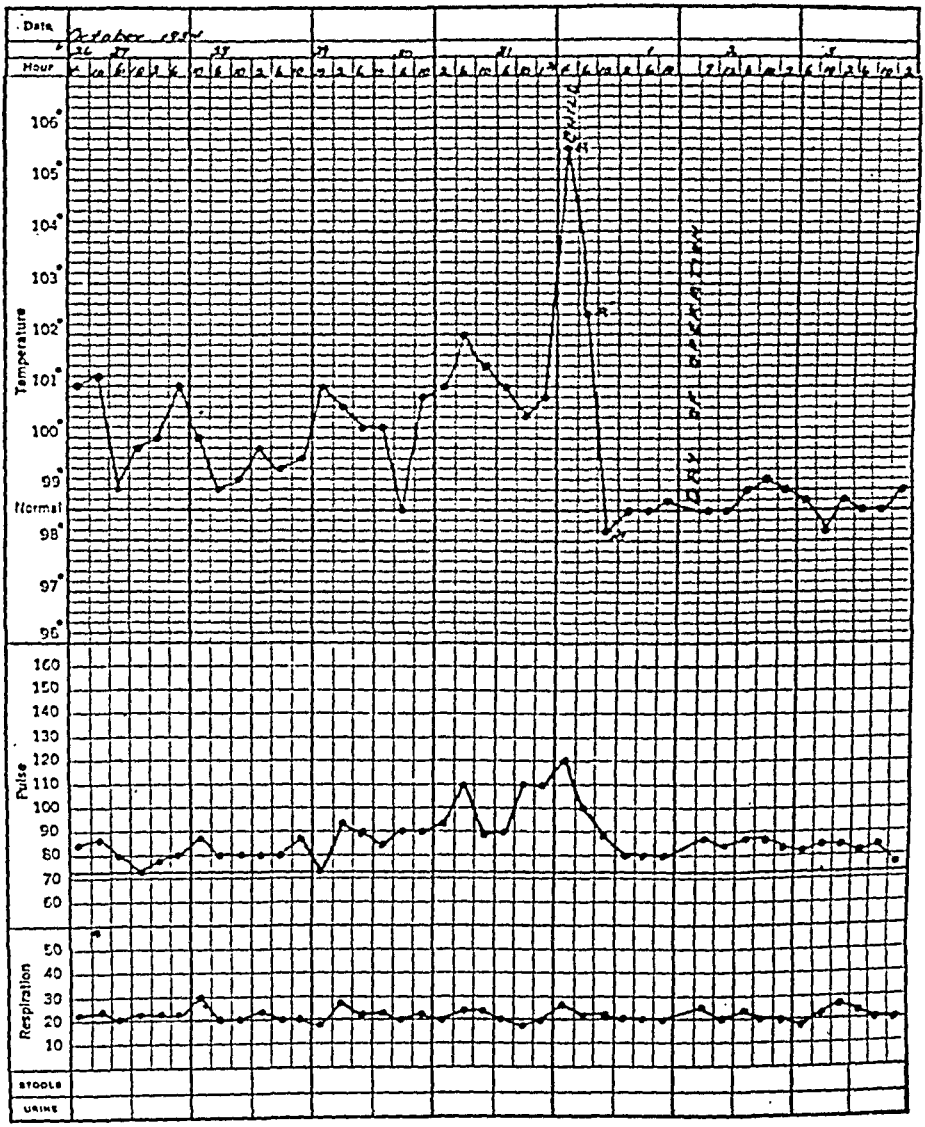


FIG. 4.—Case 4. Pre-operative chart.

rays by Dr. R. F. Kile gave the following reading: "Lung fields are clear. Heart shadow not enlarged. Spastic antrum and deformed bulb seemed rather characteristic of gall-bladder disease. The irregular filling of the rectal ampulla and sigmoid, while rather extensive, has the characteristics of a new growth." Laparotomy by Dr. Alanson Weeks showed a fixed

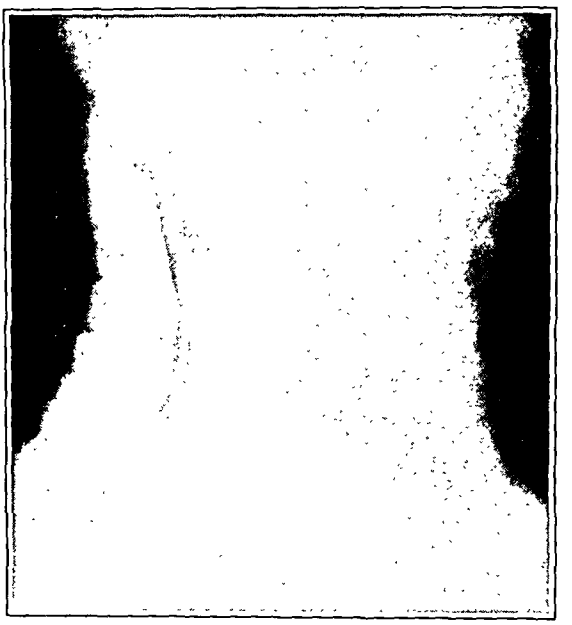


FIG. 5.—Case 1. Pre-operative Roentgen ray of colon with barium enema.



FIG. 6.—Case 2. Pre-operative Roentgen ray of colon with barium enema.

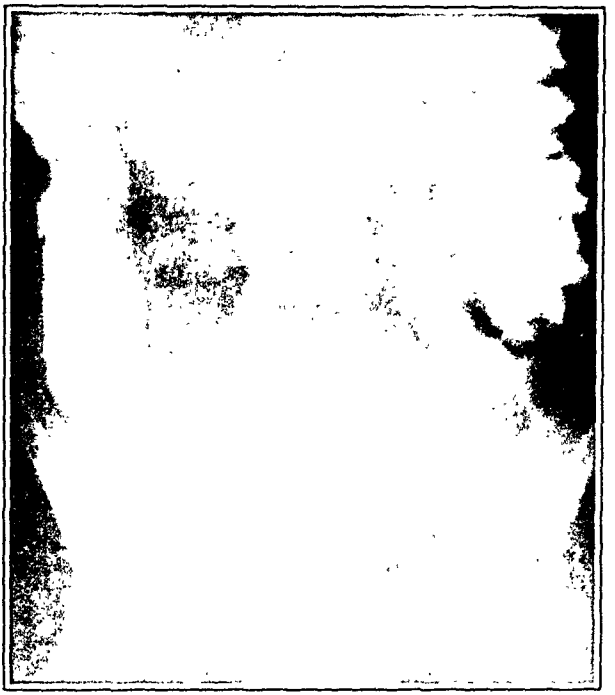


FIG. 7.—Case 3. Pre-operative Roentgen ray of colon with barium enema.

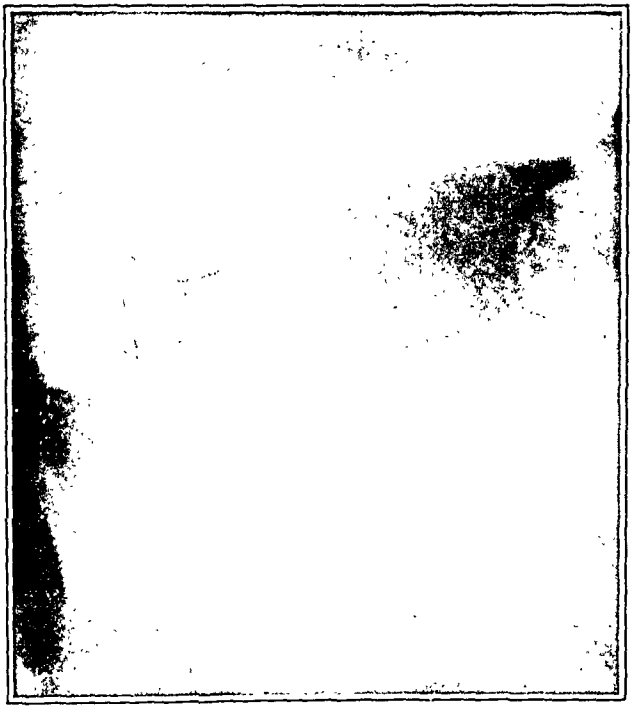


FIG. 8.—Case 4. Pre-operative Roentgen ray of colon with barium enema.

tumor of the sigmoid, 2½ inches across, and numerous hard, irregular masses in the substance of the liver. Sigmoidostomy was done to relieve obstruction.

Diagnosis. Carcinoma of sigmoid with metastases to liver. Inoperable. The patient died 6 months later, without necropsy.

SUMMARY OF CASES.

Case.			Duration of Amebiasis.	Residence.	Previous anti-amebic treatment.
1	G. L. H.	F., 49	10 yrs.	U. S., Europe, Far East	Late + + + + Emetin poisoning.
2	E. F. B.	M., 49	4 yrs.	Neb. and Calif.	None, undiagnosed.
3	J. B. F.	M., 40	7 yrs.	Pac. Coast, U. S.	Early + + + + Emetin poisoning.
4	B. A. B.	M., 48	3 yrs.	N. West, U. S.	None, undiagnosed.

Discussion. In all cases, the amebas were finally eradicated, but symptoms persisted, recurred or were intensified. In Cases 2 and 4, amebiasis had been unsuspected and untreated. In Case 1, amebiasis was discovered late and overtreated, resulting in emetin poisoning. The same result followed overtreatment early of Case 3. These 2 cases probably belong in the residual 5% of amebiasis which are resistant, require adjuvant surgical treatment or even for practical purposes are incurable.

All cases of chronic amebiasis with present or recurring dysentery or diarrhea should have Roentgen ray examination including barium enema, in order to determine early, if possible, the extent of amebic damage to the bowel and, more important, to ascertain evidence of malignancy. Certainly one should weigh the amebic factor and the patient's response to this infection against possible carcinoma superimposed upon an amebic colitis.

A careful review of such cases as No. 3 above shows the easy development of non-amebic ulcerative colitis and raises certain questions of clinical importance. Is there some predisposing factor which facilitates the development of chronic ulcerative colitis and cancer, as a sequel and complication of amebiasis? Do vitamin G and the intrinsic gastric hormone play a part in this predisposition? Is there a relationship here to the frequently noted importance of high vitamin diet in the treatment of amebiasis[10]? Does the course of the disease and the eventual occurrence of malignancy, or the obscure chronic increasing lesions of amebiasis depend on or have relation to, deficiency of vitamin G, or vitamin B? Do these same factors have any bearing on the sequential relation of cancer to amebiasis? The answers to these questions must include due consideration of the at present unexplained variations in the course of the disease produced by *E. histolytica*, variable relations between

ameba and its bacterial camp followers, and especially on the factors that make up normal resistance of the healthy colon.

Cancer may follow amebiasis by at least two known pathologic methods. (1) Chronic irritation may arise from the amebic lesion or its products, or from reactive or adventitious tissue secondary to the amebic lesion. Such irritation would be most marked at the sites of election for amebic colonization which, as has been noted, coincide with the favorite cancer areas. This does not mean that the amebic lesion is entirely responsible for such irritation inasmuch as the cancer areas are the same in non-amebic cases. It may well mean that the amebic lesions, in the presence of poorly understood predispositions, increase the facility of cancerous transition. (2) The ease with which polypoid and adenomatous growths follow amebic lesions in the colon and rectum, offers a definite added hazard because of the known ease with which such benign growths undergo cancerous change.

Summary. Four cases of amebiasis are presented, in which carcinoma of the colon followed and accompanied the amebic infection. The coincident sites of election and an overlapping of symptoms often make the differential diagnosis difficult. In at least two ways, amebic lesions may institute changes leading to cancer: by chronic irritation and by production of benign adenomas and polyps which easily become cancerous. A problem needing solution relates to possible predisposing factors which may favor development of cancer in cases of amebiasis.

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PRODUCTION OF NEPHRITIS IN DOGS BY ROENTGEN RAYS.

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Irritation of kidneys by means of Roentgen rays to produce nephritis is a procedure which has been employed by a number of investigators.[1–8] The manner in which it has been applied has varied. Most workers[1–6] have exposed the kidneys by surgical operation and irradiated them directly with medium wave length Roentgen rays. The disadvantage of this method is that treatment is usually limited to one dose and is a very drastic one. Others[8] have exposed them to high voltage Roentgen rays applied through the abdominal wall. In this manner infection of the kidneys is avoided, but irradiation is not limited to them. We have employed the method of Page,[9] in which the kidneys are transplanted to a position directly beneath the skin of the loin. After healing occurred the organs were irradiated with relatively small, repeated doses of Roentgen rays. This method has the advantage that the severity of injury may be more precisely regulated and irradiation limited to the kidneys. Simultaneous with the operation of renal transplantation, the carotid artery was sewn within a flap of skin of the neck (van Leersum method), enabling one to measure arterial blood pressure.

Method. Medium sized dogs (12 to 20 kg.) were anesthetized with amytal (isoamylethyl barbituric acid 65 mg. per kg. body weight). About 2 inches of the common carotid artery was separated from the surrounding tissues and sewn within a flap of skin. The wound beneath the loop was closed with catgut (No. 1). Collodion was poured on the wound edges and a dry cotton dressing applied. A kidney was then exposed through a lumbar incision and separated from perirenal fat without entering the peritoneal cavity. A pocket was made in the subcutaneous tissue, the kidney placed within it and the muscle layers closed beneath it with No. 1 chromic catgut. Ample space was allowed for the renal pedicle. The skin was then sutured over the kidney. This procedure was repeated on the opposite kidney. Healing of the wounds occurred usually by primary intention with 14 days. In some dogs one kidney was removed and the other transplanted. The renal pedicle was stripped of nerves in other dogs as described by Page.[9]

After a control period of about 3 weeks, during which blood pressure measurements and chemical examinations of the blood and urine were made, the dogs were anesthetized with amytal and each kidney irradiated. The irradiation was performed by Miss Christine MacDonald, as follows: The hair over the kidneys was shaved and they were carefully blocked off with sheets of lead. Two erythema doses were applied to each kidney, 26 minutes being required for each dose. A 130 kilovolt peak, 5 milliamperes, 3 mm. aluminum filter at 30 cm. distance, was employed. Most of the animals received from 5 to 7 erythema doses upon each kidney during a period of from 6 to 21 weeks.

Blood urea was ascertained by the gasometric hypobromite method of

Van Slyke and Kugel,[10] hemoglobin by the oxygen combining capacity of Van Slyke and Neill,[11] plasma proteins by Howe's method,[12] and plasma lipids by the gasometric method of Kirk, Page and Van Slyke.[13] Samples of blood were taken from the femoral artery after 24 hours fasting, but with liberal allowance of water. Heparin was used as anticoagulant. The dogs were fed the usual laboratory diet consisting of ground meat, bone and dog biscuits, throughout the experiment.

Results. Recovery from the operations of renal transplantation and preparation of the carotid loop was uneventful. Measurements of blood pressure, taken usually every 2 days for periods of about 3 weeks, showed marked variations in different animals, some being as high as 196 mm. of mercury. The pressure of individual animals seldom altered more than 40 mm. The average ranged from 120 to 170 mm. After each dose of Roentgen rays the dogs lost their appetite for a day or two but soon regained it. Their health became poor following administrations of from 4 to 6 erythema doses to each kidney. Loss of weight, loss of appetite and weakness were the most obvious signs. The urine contained protein, casts, and occasionally red blood cells. The irradiated kidneys became progressively smaller until, in some cases, they were not larger than a large walnut. The terminal stage was ushered in by vomiting, oliguria, blood in the feces and complete loss of appetite. During the last few days the dogs would not even take water. Muscular twitching was often observed. Breathing often became similar to that observed during acidosis. In one animal in which the serum CO_2 was measured one day before death, it was found to be 10.99 millimoles per liter. Some of the animals became comatose while others were conscious until within a few hours of death. During the stage of uremia, arterial blood pressure fell to 60 mm. or lower.

Autopsy showed that the kidneys were markedly shrunken, and in rare cases the capsule stripped with difficulty, leaving a scarred surface. The cortex was thinned and glomeruli could be seen. Some areas were almost completely obliterated by scar tissue. A description of the microscopic findings will not be presented, as it has already been done by Hartmann, Bollinger and Doub,[5] and more extensively by Earlam and Bollinger.[6,7] Dr. C. P. Rhoads states that the most characteristic lesion observed by him in sections of the kidneys of our dogs was hyalin necrosis of Henle's loops and proliferation of new epithelium. There was an increase in interstitial connective tissue apparently due to occlusion of the terminal bloodvessels. There was also a suggestion of proliferation of the nuclei of the glomerular capillaries with edema and thickening of the capillary wall. Dr. Rhoads has prepared a photograph which illustrates in a general way the lesions produced in our dogs.

Arterial blood pressure became somewhat elevated after irradiation in 5 of 7 dogs in which it was measured, provided the dogs were not approaching the terminal stage (Table 1).

TABLE 1.—CONSTITUENTS IN 100 CC. OF BLOOD FROM FASTING DOGS WHOSE KIDNEYS WERE TREATED WITH ROENTGEN RAY.

Dog No.	Total lipid carbon, mg.	Total lipid, mg.	Cholesterol.			Lipid amino N, mg.	Total lipid N, mg.	Lipid P, mg.	Total phosphatide, mg.	Urea N, mg.	Hemoglobin vol. % O_2 capacity.	Plasma proteins, %.	Operation on the kidneys, other than renal transplantation.	Time blood was taken before death, days.	Average blood pressure mm. Hg		Erythema doses of Roentgen ray.	Time before death after beginning treatment, weeks.
			Total, mg.	Ester, mg.	Free, mg.										Before-operation.	After operation.		
51	540	722	106	50	56	5.8	27 2	14 6	343	21.2	23.7	8.07	None	42	144	170	6	6
	782	1026	212	..	..	.	59.6	21.8	512	71.6	24.8	9.41	None	1				
41	462	601	72	36	36	12.6	31.2	15.4	362	16.2	14.3*	7.26	None	49	160	210	6	13
	710	923	172	115	57	8 7	55.8	15.7	369	134.4	17.4	6.94	None	5				
7	1226	1594	286	179	107	9 0	54.0	16.5	388	150.2	28.2		Nephrectomy denervation	2 hrs.	164	180	5	12
11	1013	1317	320	196	124	23.0	114.3	20.8	489	301.8	26.1		Nephrectomy denervation	1	120	122	4	7
21	469	610	203	131	72	14.1	64.0	7.4	174	158.5	..	..	None	..	140	172	8	21
23	454	590	103	46	57	3.7	11.9	8.7	204	58.2	..	..	None	35	136	148	8	9
	589	766	..	..	..	..	..	..	..	94.5	..	..	None	20				
	756	983	216	..	..	..	..	..	..	174.3	23.1	..	None	5				
1	371	482	148	76	72	6.9	33.2	6.4	150	..	..	7 38	Nephrectomy	5	170	200	5	9
Control	611	794	165	70	95	6.2	4.4	13.9	327	..	..	..	Both kidneys denervated	..	196			
Control	875	1137	152	36	116	7.8	6.5	20.6	484	..	..	..	Both kidneys denervated	..	154			
Control	540	702	170	108	62	5.8	..	18.0	423	10.6	19.0	..	Normal	..	130			
Control	663	861	194	124	70	5.8	38.1	18.2	428	13.6	18.7	7.25	Unilateral nephrectomy	..	136			

* Low value probably due to blood loss during operation.

Observations on some chemical changes in the blood were made (Table 1). Hemoglobin was increased somewhat, especially during the terminal stage. Probably this was due to hemoconcentration, since the plasma proteins also rose (Dog 51). Nephritis produced by Roentgen rays differs sharply in this manner from Bright's disease in human beings, for in the latter anemia is one of the most characteristic signs.



FIG. 1.—Section of dog's kidney treated with Roentgen rays showing interstitial sclerosis, avascular glomeruli with nuclear proliferation, cell rests representing tubules which have atrophied, and perivascular sclerosis.

The urea nitrogen rose in all the animals, especially during the terminal few weeks. In one (No. 11) it reached the very high value of 302 mg.%.

The behavior of the plasma lipids was similar to that observed in patients suffering from the terminal stage of chronic hemorrhagic Bright's disease found by Page, Kirk and Van Slyke.[15]

Except in those dogs where marked hemoconcentration had occurred, the total lipids, total ester and free cholesterol and lipid phosphorus did not differ from normal dogs on the same diet. Where marked concentration of the blood occurred (Nos. 7 and 11)

total lipid, total free and ester cholesterol, and lipid amino nitrogen were moderately elevated. Just as in human blood, as observed by Van Slyke, Page, Kirk and Farr,[14] dogs' blood contained a substance (or substances) which is soluble in petroleum ether, containing amino groups in greater proportion to phosphorus than the 1 to 1 ratio present in cephalin.

The total lipid nitrogen rose markedly, but not parallel with the rise in urea nitrogen. For example, one analysis showed urea nitrogen to be 72 mg. %, and lipid nitrogen 60 mg. %, while another showed urea nitrogen 150 mg. %, and lipid nitrogen 54 mg. %. Lipid nitrogen evidently rises progressively during the course of renal insufficiency produced by Roentgen rays independently of urea nitrogen.

Summary. Chronic injury localized to the kidneys of dogs has been accomplished by transplanting the kidneys to the flank beneath the skin, and, after healing, irradiating them with Roentgen rays. The tissues lateral to the kidneys were protected by lead plates. Repeated doses of Roentgen rays have been given in order to secure chronic, progressive lesions. These lesions have been described adequately by others,[5–7] and consist largely, as we can confirm, of tubular damage with usually less extensive glomerular changes. Nephritis produced in this manner leads to death in the course of a few months, with symptoms typical of renal failure.

The following changes in the chemical composition of the blood have been noted: Slowly progressive but independent rise in urea nitrogen and total lipid nitrogen, and maintenance of total lipids, total, free and ester cholesterol, lipid amino nitrogen and lipid phosphorus, within limits normal for dogs on the same diet. These data closely resemble those found by Page, Kirk and Van Slyke[15] to be typical of the terminal stage (urea clearance less than 20% of normal) of hemorrhagic Bright's disease in man. They differ in that hemoconcentration occurred in the dogs with a corresponding increase in plasma proteins, hemoglobin and, to a less marked degree, the plasma lipids. They differ further in that anemia, which is regularly observed in human nephritis, did not occur in the dogs with Roentgen ray nephritis.

Just as in human blood, dog's blood contains substances, soluble in petroleum ether, containing amino groups in greater proportions in phosphorus than the 1 to 1 ratio present in cephalin.

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CREATINURIA IN ADULT MALES.*

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The presence of creatin in the urine of children in the prepuberty period and of normal adult women has been a generally accepted fact. Its occurrence in the urine of normal adult males has not been so accepted. Folin and Dennis[1] reported its occurrence in the urine of a 17-year-old boy. Rose[2] and Harding and Gaebler[3] regard 15 to 16 years as the limiting age at which creatin fails to be normally excreted in the urine of males.

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In the course of investigations on the partition of the nitrogenous constituents of urine, during the past 3 years, the presence of creatin as determined by difference between preformed and total creatinin was found in the urine of both normal subjects and hospital patients, including a large number of adult males.

Our interest was further stimulated by the interesting papers of Light and Warren,[4] who report the occurrence of creatin in the urine of 35 out of a total of 81 boys between the ages of 14 and 19. These authors present data to show a diminishing incidence with age. The amount of creatin found in the 24-hour samples varied from 15 to 229 mg.

These observations of Light and Warren, together with our own experience led to a study of creatinuria in a group of somewhat older normal male subjects.

Experimental. Ten male medical students between the ages of 20 and 24, and 5 adult male members of the laboratory staff, were studied. All subjects were forbidden any *unusual* exercise but were allowed to carry on the daily routine in their usual way. No restrictions as to diet were made. A record of the diet was kept and in no instance was it at all unusual. All subjects were free from low-grade infections or diseases which might occasion an increased temperature or basal metabolic rate. No history of nephritis, cardiac disease, or muscular abnormality was present. The 24-hour urine specimen was collected over the usual preservative used in this laboratory of 10 ml. acetic acid and 5 ml. chloroform. Blank control experiments were run on reagents and preservative, and in later studies toluene and chloroform were substituted for the acetic acid-chloroform preservative to rule out any possible interference from this source.

Analyses for both preformed and total creatinin were made in duplicate on each urine by the method of Folin.[5] Both the methods of autoclaving and of boiling were used for the determination of total creatinin. Results by both the latter procedures checked consistently within the experimental errors of the two methods, *viz.*, approximately 10 mg. for the 24-hour sample. The results by boiling were always somewhat lower than those obtained by autoclaving.

From the results obtained (Table 1) it would appear that amounts

TABLE 1.—CREATINURIA IN NORMAL MALES.

Subject.	Age.	Weight, lbs.	Height, in.	Total nitrogen.*	Preformed creatinin nitrogen.*	Creatin nitrogen.*
T. T. H.	20	175	69.5	19.30	0.725	0.018
E. H.	21	148	69.0	16.08	0.669	0.091
L. G.	22	175	70.0	17.85	0.830	0.000
J. T. H.	22	170	73.0	15.45	0.756	0.071
H. P. P.	22	140	70.0	13.10	0.664	0.048
A.	22	146	70.5	13.58	0.645	0.043
H.	22	170	68.0	12.92	0.606	0.122
H. W.	22	140	70.0	16.35	0.491	0.010
C. N.	23	180	70.0	14.48	0.519	0.028
J. P.	23	155	75.0	15.45	0.748	0.025
T. H. H.	29	165	72.0	12.68	0.702	0.065
E. F.	29	165	71.5	13.08	0.695	0.057
W. B. C.	33	134	68.0	10.90	0.512	0.042
J. R.	30	120	65.0	11.28	0.531	0.058
F. H. L. T.	34	126	68.0	10 67	0.511	0.091

* All values expressed as gm. excreted in 24 hours.

of creatin varying between 10 and 100 mg. in 24 hours are present in the urines of most of the normal males in the group of 16 subjects studied. Variations in the amounts excreted by the group of the third decade are much wider than those of the fourth.

Data obtained on 3 patients, who were confined to bed at the time these observations were made, are given in Table 2. The same

TABLE 2.—CREATINURIA IN PATIENTS ABOVE 35 YEARS OF AGE.

Patient	Diagnosis.	Sex.	Date.	Remarks.	Total nitrogen, gm.*	Total creatinin nitrogen, gm.*	Creatin nitrogen, gm.*
D	Leukemia	Female	3/13/33	Elevated B.M.R.	11.00	0.299	0.112
			3/20/33		10.30	0.312	0.056
			3/22/33		9.22	0.297	0.000
W	Obesity	Male	5/31/33	Standardized diabetic diet. Limited exercise.	8.93	0.455	0.069
			6/ 2/33		11.55	0.576	0.060
			6/ 3/33		15.30	0.640	0.028
			6/ 5/33		13.40	0.567	0.038
			6/ 9/33		12.19	0.514	0.011
S	Addison's disease	Female	5/20/33	. .		0.326	0.092
			5/21/33	. . .		0.284	0.032
			5/23/33			0.290	0.045
			5/26/33	. . .		0.289	0.028
			6/24/33			0.304	0.060
			6/25/33			0.318	0.058
			6/26/33			0.294	0.055

* All values expressed in gm. excreted in 24 hours.

precautions and technique were followed in every instance. It will be observed that the values for urine creatin nitrogen in the case of 2 female subjects are of the same order of magnitude as those found for normal males. It is of interest, also, that marked variations occur in the output of creatin from day to day. It is probable that, in subjects in whom no creatinuria is found, serial analyses would show the presence of this substance in variable amounts. Variations in the creatin nitrogen values of the 3 patients occurred during the time that they were confined to bed. It seems quite possible that had Light and Warren followed their subjects while confined to bed for a longer period of time they would have encountered considerable fluctuations in the amount of creatin excreted in the urine.

Table 3 shows the daily excretion of creatin in a normal male adult of 33 years at frequent intervals. The diet was uncontrolled except for the addition of a constant amount of nucleoprotein for other experimental purposes. The nucleoprotein used was repurified yeast nucleic acid which is not known to cause an increase of exogenous creatin. It is sufficient to remark here that the excretion of

other nitrogenous substances was essentially such as would be expected from the regimen used. It is particularly interesting to note that on November 18 and 19, while the subject was immobilized in bed following a fracture, the creatin excretion in the urine was markedly diminished. Eighteen days later, 5 days after resumption of usual activity, the creatin in the urine was still 2 to 3 times as great as that usually found in this subject.

While the preformed creatinin remained essentially constant, extreme variations occurred in the urine creatin. On one occasion an increase was probably due to extreme muscular activity. However, other variations from 48 to 190 mg. in 24 hours could not be accounted for on this basis.

With the expectation that variations in the food intake might account for some of the unexplained increase in creatin, an experiment was devised to study the creatin output while on a minimum nitrogen intake. Two normal male subjects were chosen (F. H. L. T. and W. B. C.). One who engaged in no great muscular activity and one who normally took considerable exercise and who carried on his usual activities during the experiment. After a preliminary control period of unrestricted hospital diet both subjects were placed on the same experimental diet. The diet provided approximately 2800 calories chiefly in the form of carbohydrate and fat, the protein being restricted to from 2 to 3 gm. a day. The fat was in the form of olive oil and butter. The protein was derived from an ounce of cream and a teaspoonful of potatoes daily. The chief source of carbohydrate was orange juice saturated with cane sugar. Fresh greens, vinegar, salt and so forth, were permitted as desired.

The urines were collected in the way described above. A partition of the urine nitrogen constituents was made (Table 4). It will be noticed that the preformed creatinin remained essentially the same, although the urea and total nitrogen fell to the minimum limits. During the last 4 days the urine creatin reached a constant figure in both subjects.

It is noteworthy that the urine creatinin in the second subject (W. B. C.) rose slightly during the restricted protein period. On February 11, 1934, this patient spent a day skiing. The low volume of urine on this day was due to excessive perspiration. An increase in creatin followed and was still present 2 days later.

In the case of the first subject there was a slight diminution of the creatin over the 15-day experimental period. In general in this experiment there seems to be a relative independence of the basal amount of creatin in the urine to the protein intake. It must be remembered, of course, that both of these subjects were receiving sufficient protein to protect the body proteins.

Discussion. It appears from the foregoing protocols that creatin may appear in the urine of normal adult males in detectable amounts. While it is true that in some cases the amount of creatin present is

TABLE 3.—SUBJECT T.

Age.	Sex.	Height, in.	Weight, lbs.	Diet.	Urine volume, ml.	Specific gravity.	Total nitrogen,* gm.	Preformed creatinin nitrogen,* gm.	Creatin nitrogen,* gm.	Date.	Remarks.
33	Male	68	126	Usual hospital diet	2200	1.015	13 56	0.580	0.015	11/18/33	Convalescent, in bed, from fracture of wrist.
					1550	1.017	13.00	0.554	0.027	11/19/33	
					2360	1.009	13.72	0.508	0.191	11/23/33	Restricted floor privileges.
										11/26/33	Discharged from hospital.
				Uncontrolled diet	2800	1.013	15.30	0.562	0.125	12/ 5/33	Usual activity.
					2240	1.015	14.95	0.504	...	12/ 7/33	Usual activity.
					2310	1.025	13.65	0.496	0.196	12/11/33	Usual activity.
				+10 gm. daily nucleic acid	3125	1.021	15.15	0.582	0.033	12/14/33	Usual activity.
					2220	1.021	12.20	0.485	0.017	12/19/33	Usual activity.
					3000	1.020	14.15	0.529	0 178	12/21/33	Violent exercise.
				+10 gm. daily hydrolyzed nucleic acid	1380	1.028	11.25	0.500	0 068	12/26/33	Usual activity
					1750	1.026	10.67	0.511	0.091	12/28/33	Intermittent diarrhea from medication ingested.
					1450	1.025	9.68	0.188	0.053	1/ 4/34	

* All values in gm. per 24 hours.

TABLE 4.—CREATINURIA WITH MINIMUM NITROGEN INTAKE.

Subject.	Age.	Weight, lbs.	Height in.	Diet.	Date.	Volume, ml.	Specific gravity.	Uric acid nitrogen,* gm.	Urea nitrogen,* gm.	Preformed creatinin nitrogen,* gm.	Creatin nitrogen,* gm.	Ammonia nitrogen,* gm.	Amino acid nitrogen,* gm.	Total nitrogen,* gm.	Residual nitrogen,* gm.
F. H. L. T. .	33	126	68	Ordinary hospital house diet	12/14/33	3125	1.021	0.350	12 880	0.582	0.057	0.435	0.357	15.150	0.503
					12/26/33	1380	1.028	0.209	8.630	0.500	0.068	0.224	0.158	11.250	1.369
					1/28/34	1750	1.026	0.218	8.980	0.511	0.091	0.329	0.156	10.670	0.385
				Total calories, 3000. Protein restricted to 3 gm. daily	2/ 1/34	1450	1.025	0.168	8.230	0.408	0.053	0.232	0.092	9.680	0.497
					2/ 8/34	2310	1.008	0.212	2.730	0.455	0.031	0.423	0.090	5.590	1.649
					2/11/34	2410	1.006	0.197	2.040	0.579	0.091	0.274	0.126	5.210	1.903
					2/13/34	1620	1.012	0.161	1.440	0.480	0.032	0.265	0.064	3.620	1.078
					2/15/34	1340	1.017	0.170	0.820	0.522	0.038	0.352	0.032	3.860	1.926
W. B. C. . .	33	134	68	Ordinary hospital diet	12/14/33	2230	1.014	0.179	9.150	0.512	0.042	0.382	0.068	10.990	0.657
					12/26/33	1590	1.016	0.142	11.600	0.567	0.054	0.415	0.120	14.600	1.602
					1/28/34	1660	1.021	0.175	11.520	0.590	0.088	0.314	0.212	14.320	1.421
				Total calories, 3000. Protein restricted to 3 gm. daily	2/ 6/34	2230	1.012	0.222	3.310	0.573	0.047	0.060	0.074	4.210	0.000
					2/ 8/34	1870	1.014	...	2.320	...	...	...	...	5.160	
					2/11/34	900	1.026	0.158	1.870	0.660	0.073	0.154	0 076	2.910	0.000†
					2/13/34	1560	1.013	0.188	1.770	0.563	0.182	0.212	0.072	3.970	0.983†
					2/15/34	2000	1.017	0.267	1.350	0.596	0.088	0.366	0.144	4.350	1.575
					2/18/34	1250	1.021	0.168	1.520	0.592	0.094	0.178	0.098	3.120	0.564

* Values as gm. per 24 hours. † Exercise.

but 10% of the total creatinin, it will be observed that the difference is always positive, and two methods for determination have been used. The amount of creatin so found varies markedly from day to day. In many male patients under observation the creatin in the urine fluctuates from zero to 100 mg. per 24 hours. This finding may account for the fact that creatin determinations on a single 24-hour specimen may give negative results. In one individual whose urine has been analyzed at frequent intervals over the past 5 years creatin has been found in varying amounts. The latest data on this subject (Table 3) show amounts varying between 50 and 175 mg. in 24 hours, with only slight changes in the creatinin during normal activity. It is of some interest to note that this subject showed a much diminished creatin after confinement to bed for 10 days. The excretion of creatin was much increased after limited floor privileges were restored, and was still elevated 18 days later. This is not always the case, however, because many patients, both male and female, who have been hospitalized with complete bed rest for weeks do not always show progressive decrease of creatinuria, although they may show some increase after discharge. Patient W. (Table 2), however, showed such progressive decrease in creatin in the urine during the few days of complete bed rest.

Experimental work on children and dogs[6,7,8,9,10] has shown increases in the urinary creatin with increased protein intake. In an attempt to discover whether the creatinuria in the 2 adult male subjects studied was due to exogenous creatin, a restricted protein diet was used with the results given above. The two points of interest in the experiments were that both subjects maintained a creatinuria, although the total nitrogen output was reduced to minimum limits and that in 1 patient following exercise a somewhat elevated output was found. These data are confirmatory also of the endogenous nature of creatinin and creatin and to some extent indicate their relationship to health and muscular activity.[4,11,12]

Thus the data presented indicate that creatin occurs in small amounts in the urines of some adult males, either continuously or occasionally. There is some evidence confirmatory of the findings of Light and Warren[4] that at least some portion of the creatinuria may be due to changes in the degree of muscular activity or the performance of *unusual* muscular work. The amounts of creatin usually found are within the ranges found by these authors. The incidence of creatinuria in normal adult males was not determined as the series was too small. That it did occur in such a high percentage of the individuals studied may be chance. It should be pointed out, however, that the variations of creatin in the urine of a given individual are so marked that more than one determination should be made before reporting the complete absence of this substance.

Summary. 1. Creatin has been found in the urine of 15 adult males in amounts varying between 0 and 196 mg. of creatin nitrogen per 24 hours.

2. This amount of creatin was not materially changed by marked restriction of the protein intake.

3. Some data are presented suggesting that unusual muscular activity or sudden change in muscular activity may result in an increase of the creatin excreted.

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THE FILTERABLE CALCIUM OF BLOOD SERUM.

I. A COMPARISON OF FILTERABLE CALCIUM OF SERUM AND TOTAL CALCIUM OF CEREBROSPINAL FLUID IN NORMAL, HYPERPARATHYROID, AND HYPOPARATHYROID STATES.

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RONA and Takahashi[1] showed that part of the serum calcium is diffusible and part non-diffusible. Numerous investigators [2–9] have confirmed and extended these observations, and, as a result, normal values for a number of species, including man, have been established.

Cameron and Moorhouse[10] suggested that spinal fluid calcium represents the filterable calcium of plasma. This theory was based on the assumption that the capillary wall and the endothelial membrane of the choroid plexus form a more nearly perfect semipermeable membrane than any artificial one. Merritt and Bauer[11,12] also supported this point of view, and Cantarow,[13,14,15] apparently satisfied that it is correct, has reported spinal fluid calcium values as filterable calcium of serum in a variety of pathologic conditions.

It is true that most comparative studies of serum and spinal fluid calcium have demonstrated that the filterable calcium of the former very closely approximates the total calcium of the latter, but in certain instances the differences have been too large to be accounted for by experimental error.[16]

Only 4 cases of hyperparathyroidism in which observations on the filterable calcium had been made could be found in the literature. Snell[17] reported one determination of the total and filterable serum calcium in a case of hyperparathyroidism. The filterable calcium percentage of the total was within normal limits, and the amount of filterable calcium (6.1 mg. %) was less than that in one of the controls (6.3 mg.%). Benjamin and Hess,[18] who introduced the concept that the serum calcium exists in four fractions, two diffusible and two non-diffusible, reported studies on one case of hyperparathyroidism. The sum of their "filterable" and "ionized" fractions, which is equivalent to the diffusible or filterable fractions of other authors, was found to be increased. Herbert[19] has studied the total and diffusible serum calcium in 2 cases of undoubted hyperparathyroidism. Her studies of diffusible serum calcium were made at long intervals, and in each case there was but one comparison of the cerebrospinal fluid calcium and the diffusible serum calcium. In both cases there was an increase in the filterable serum calcium, and the spinal fluid calcium, although slightly elevated, was significantly less than the filterable serum calcium. Two determinations of the spinal fluid calcium on the same patient, made at an interval of 6 weeks, both of which gave the same result, suggests that time is not the factor responsible for the difference between the values for diffusible serum calcium and spinal fluid calcium. Herbert's 2 cases of osteitis fibrosa, in which the serum calcium and inorganic phosphorus values were normal, do not conform to the commonly accepted diagnostic criteria of hyperparathyroidism.

Very few comparative studies of the spinal fluid calcium and filterable serum calcium in cases of hyperparathyroidism and hypoparathyroidism have been reported, and in only 1 case of hyperparathyroidism (Herbert) have repeated determinations been made. For these reasons, daily simultaneous determinations of total and filterable serum calcium and spinal fluid calcium were made in 2 cases of hyperparathyroidism and 2 of hypoparathyroidism in the endeavor to ascertain whether there was any variation in the spinal fluid calcium and filterable serum calcium over a period of weeks.

In all previous studies of the spinal fluid calcium, particularly those dealing with comparisons between filterable serum calcium and total spinal fluid calcium, the authors have apparently assumed that the spinal fluid calcium is completely filterable. We have considered it desirable to test this assumption experimentally.

Material. Patients on the Neurologic Service who were free from organic disease of the central nervous system which might affect the permeability of the membranes of the chorioid plexus (*i. e.*, as attested by normal spinal fluid under normal pressure) were used as controls.

Characteristic generalized roentgenographic changes in the bones, high serum calcium, low serum inorganic phosphorus, high serum phosphatase and hypercalcinuria were the diagnostic criteria of hyperparathyroidism. Additional proof of the correctness of the diagnosis in 1 case (G. J.) was afforded by the abrupt fall in serum calcium following removal of a parathyroid adenoma.*

The validity of the commonly accepted criteria of hyperparathyroidism (hypercalcemia, hypercalcinuria, hypophosphatemia) has recently been questioned by Robbins and Kydd,[20] who state that they have found similar abnormal phosphorus and calcium values in 3 cases of multiple myeloma and 1 case of Paget's disease (osteitis deformans). Previously Bauer[21] and Compere[22] had been unable to demonstrate these changes in Paget's disease. In our work we have adhered to the diagnostic criteria accepted by most investigators.[21,22,23]

A history of convulsions following thyroidectomy, strongly positive Chvostek's and Trousseau's signs, low serum calcium, and high inorganic phosphorus served as the basis for the diagnosis of hypoparathyroidism in 1 of our cases (O. C.). The appearance after thyroidectomy of mild tetany, a feeling of numbness in the upper extremities, inability to relax, a positive Chvostek's sign, and low serum calcium established the diagnosis in the second case of hypoparathyroidism (C. E.).

In 1 case (O. C.) a single determination was made at the end of a 6 months' period of calcium and parathyroid extract administration; treatment was then discontinued, and thereafter repeated determinations were made until tetany supervened and after specific treatment had been resumed. In the other case (C. E.) the estimations were made 3 months after thyroidectomy, during which time no treatment had been administered, and again after the institution of treatment with calcium and parathyroid extract.

Methods and Experimental Procedure. Approximately 25 cc. of blood were removed from a vein in the usual manner. Venipunctures were done without regard to meals except when inorganic phosphorus was to be estimated, in which case the sample was taken after a fast of 12 to 14 hours.

* Since this article was submitted for publication, the diagnosis of hyperparathyroidism has been proved in the case of E. W., by the removal of a parathyroid adenoma, with the resulting rapid return to normal of the blood calcium and phosphorus values.

Cerebrospinal fluid was obtained either by lumbar or cisternal puncture not more than 5 minutes before the venipuncture.

Clark and Collip's[24] modification of Tisdall's[25] method was used for all calcium determinations. Inorganic phosphorus was estimated by the method of Fiske and Subbarow.[26] The method of Andersch and Gibson[27] was used for total protein. All determinations were done in duplicate except when accident prevented. Eighty-five per cent of the duplicates of the filterable calcium checked within 5%, and the remainder checked within 10%. The calcium of the ultrafiltrate was recalculated according to the formula given by Benjamin and Hess[18] to correct for the quantity of protein in the serum.

Collodion sacs were prepared from Mallinckrodt's parlodion by Greenberg and Gunther's[4] method. To avoid the possibility of error due to passage of protein into the filtrate, all filtrates which gave a positive biuret test were discarded. The permeability of the membranes to calcium chlorid solutions was tested frequently and always found to be complete. The close agreement between calcium values of ultrafiltrates obtained from the

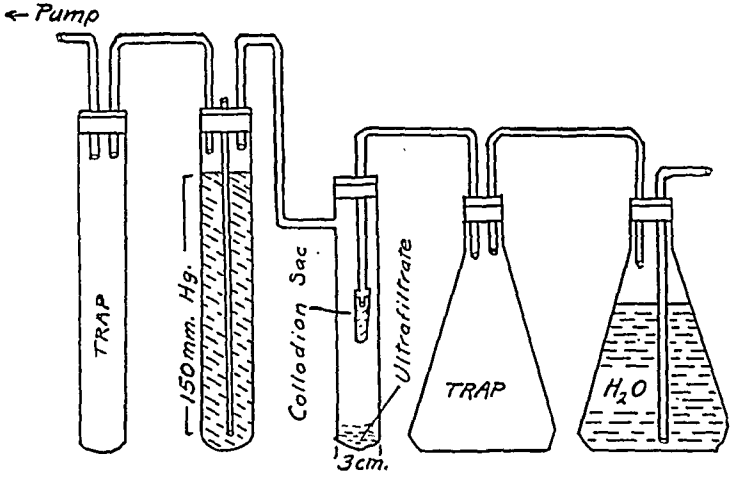


FIG. 1.—Schematic drawing of ultrafiltration apparatus.

same serum by filtering through different membranes also served as a check on the permeability of the membranes. All sacs were discarded after being used once. An ultrafiltrate of the serum was obtained by the method of Greenberg and Gunther,[4] which is essentially the one described by Updegraph, Greenberg, and Clark.[8] Several minor modifications were made to simplify the apparatus and to insure more rapid filtration (Fig. 1). If 7 to 8 cc. of serum be used in each sac, 2 cc. of filtrate are obtained in 2 hours.

Results. Tables 1, 2, and 3 summarize our results for total serum calcium, filterable serum calcium, and spinal fluid calcium in a group of normal individuals, in 2 cases of hyperparathyroidism, and 2 cases of hypoparathyroidism, respectively.

Discussion. It may be seen from Table 1 that the values for filterable calcium of blood serum are within the normal limits reported by others.[5,8,18,19] Furthermore, the results indicate that over the normal range of serum calcium values the filterable calcium of the serum and the calcium of the spinal fluid are approximately

the same, as Searle and Michaels[28] have shown. In 2 normal subjects (L. and R., Table 1), however, the difference between the filterable calcium of the serum and the calcium of the spinal fluid

TABLE 1.—CALCIUM STUDIES IN A GROUP OF NORMALS.
(ALL CALCIUM VALUES IN MG. %.)

Patient.	Date.	Serum calcium. Total.	Serum calcium. Filterable.	Spinal fluid calcium. Total.	Spinal fluid calcium. Filterable.	Serum protein, %.
H	12- 7	10.4	5.2	...	...	6.2
F	12- 8	10.6	4.3	4.7	4.8	5.0
W	12-13	11.0	4.9	5.3	5.1	7.4
L	12-13	10.1	5.3	4.7	4.6	7.3
M	12-13	11.3	3.3	...	...	6.0
M	12-15	11.4	3.5			
M	12-19	10.0	4.2			
C	12-20	10.4	4.8	4.9	...	5.8
H	12-20	10.4	5.6	5.5	...	6.3
R	1- 4	10.2	5.3	4.4	...	5.2
T. R. . . .	1- 4	9.2	5.5	4.8	...	5.6

TABLE 2.—CALCIUM STUDIES IN 2 CASES OF HYPERPARATHYROIDISM.
(ALL CALCIUM VALUES IN MG. %.)

Patient.	Date.	Serum calcium. Total.	Serum calcium. Filterable.	Spinal fluid calcium. Total.	Spinal fluid calcium. Filterable.	Serum protein, %.
E. W. . . .	11-22	15.3				
	12- 8	16.5				
	12-10	16.2	6.9	5.8	...	7.0
	12-12	15.4	...	...	...	7.7
	12-13	15.3	5.8	6.0	6.1	6.9
	12-14	15.7	7.3	...	...	7.4
	12-15	15.0	7.1	...	...	7.0
	12-17	16.2	7.8			
	12-18	16.5	7.3	5.6		
	12-19	14.9	6.5	...	...	7.0
	12-20	15.4	6.8	5.9	6.0	7.2
	12-21	14.1	6.9	6.4	6.3	6.9
	12-31	16.3	7.1	5.5		
	1- 2	14.3	8.0			
	1- 3	15.2	8.1			
	1- 5	15.0	7.8	...	...	7.0
	1-25	15.6	8.7			
Average . . .	...	15.3	7.2	5.8		
G. J.	12-31	12.3	7.3	4.4	4.6	5.2
	1- 1	12.7	7.1	...	...	5.2
	1- 2	12.7	6.9	...	...	5.4
	1- 3	12.9	7.5	...	...	5.4
	1- 4	13.1	7.7	5.0	5.2	
	1- 5	14.6	7.6	...	...	5.4
	1- 7	12.3	7.0	4.8		
Average . . .	...	13.0	7.3	4.8		
	2-20*					
	2-20†	11.8				
	2-21	10.2				
	2-22	8.4				
	2-23	7.4	3.4			
	3- 1	7.3	3.4			
	3- 6	7.2	3.4			
	3-11	7.2	3.6			
	3-12	6.7	2 S.	4.7		

* 8 A.M. Removal of proven parathyroid adenoma.
† 4 P.M.

TABLE 3.—CALCIUM STUDIES IN 2 CASES OF HYPOPARATHYROIDISM. (ALL CALCIUM VALUES IN MG. %.)

Patient.	Date.	Serum calcium.		Spinal fluid calcium, total.	Serum protein, %.	Remarks.
		Total.	Filterable.			
O. C.	1–15	7.6	3.4	...	5.6	After 6 mos. on calcium and parathyroid extr., which was discontinued on this date.
	1–17	6.1	2.3	3.7	5.6	
	1–18	6.5	2.4			
	1–19	6.3	2.3	4.8	5.6	
	1–21	6.1	2.4			
	1–22	5.6	1.9	4.2	5.4	Tetany; 4 cc. parathyroid extr. and 5 gm. calcium lactate daily started and continued to 2–5.
	1–23	6 2	2.3	...	5.4	
	1–25	6.7	2.9	4.3	5.6	
	1–28	8.2				
	1–31	7.6	3.5	...	5 2	
	2– 5	7.4	3.0	...	5 2	
C. E.	3– 4	6.1				
	3– 6	5 8	2.5	...	5 6	
	3– 7	6.1	2 3	4 1	5.6	
	3–11	5 4	2 3	3 9		
	3–15	...	...	..	...	5 gm. calcium lactate and 1 cc. parathyroid extr. daily started.
	3–20	7 0	4.7			
	3–21	7.0	4.2			
	3–25	7.8	4.2			
	4– 3	7.5				
	4– 6	...	. .	..	...	Parathyroid extr. 3 cc. daily.
	4– 3	7.5				
	4–11	9.9				
	4–22	9.2	5 5	3.9		

is greater than the experimental error. The cerebrospinal fluid values, which varied between 4.4 to 5.5 mg.%, are in close agreement with the normal spinal fluid calcium values of 4.5 to 5.5 mg.% reported by Cantarow[13] and Searle and Michaels.[28]

In 1 case of hyperparathyroidism (E. W.), in which the total calcium averaged 15.3 mg.%, the filterable calcium of the serum averaged 7.2 mg.% (range 5.8 to 8.7 mg.%) over a period of 2 months, which is definitely higher than normal. Six estimations of spinal fluid calcium varied from 5.5 to 6.4 mg.%, averaging 5.8 mg.%, which, although very slightly elevated, is considerably lower than the average (7.2 mg.) for filterable calcium of serum in this case.

In the second case of hyperparathyroidism (G. J.), in which the total serum calcium averaged 13.0, the filterable calcium averaged 7.3 mg.%. The spinal fluid, however, was consistently within normal limits, varying between 4.4 and 5 mg.%. The results in these 2 cases of hyperparathyroidism are in agreement with those

obtained by Merritt and Bauer[11] after administering parathyroid extract to normal human beings, and with the results in 2 cases of hyperparathyroidism reported by Herbert.[19]

Since all our observations were made over a considerable period of time, it follows that the lack of correlation between filterable serum calcium and cerebrospinal fluid calcium is not due to failure of the cerebrospinal fluid calcium to reach an equilibrium with the calcium of the blood serum, as has been suggested by Greenberg.[29]

It should be noted also that the correct relationship between cerebrospinal fluid calcium and filterable serum calcium cannot be arrived at if only single comparisons are made, since there are independent fluctuations in the two. For example, in the case of E. W. there was perfect agreement on one day (5.8 and 6), and considerable disparity on another (7.3 and 5.6).

In his contention that ankylosing (rheumatoid) polyarthritis may be due to hyperparathyroidism, Funsten[30] has not demanded permanent elevation of the serum calcium as a necessary criterion of hyperparathyroidism. The serum calcium in our 2 cases of hyperparathyroidism was invariably elevated. This is in agreement with the results of other investigators.[21,23]

After taking 1 cc. of parathyroid extract and 60 grains of calcium lactate daily for several months, 1 patient (O. C.) with hypoparathyroidism had a total serum calcium of 7.6 mg.% and a filterable calcium of 3.4 mg.%. After the parathyroid extract and calcium were discontinued there was a progressive fall of both the total and filterable calcium values. On the sixth day the total serum calcium reached 5.6 mg.% and the filterable calcium 1.9 mg.%, and the patient showed definite signs of tetany (spontaneous carpopedal spasm). In contrast to this fall in the filterable calcium of serum, the cerebrospinal fluid calcium rose slightly from 3.7 to 4.8 mg.%. At this point the daily administration of 4 cc. of parathyroid extract subcutaneously and 60 grains of calcium lactate orally was begun. The total and filterable calcium rose progressively, but the latter never reached the level of the spinal fluid calcium. After 2 weeks of this therapy the total serum calcium was only 7.4 mg.% and the filterable calcium was 3 mg.%.

In the second case of hypoparathyroidism (C. E.) the total and filterable calcium were much diminished, whereas the spinal fluid calcium was essentially normal. Parathyroid and calcium therapy caused the total serum calcium to rise essentially to a normal level and the filterable calcium to return to a high normal value. The spinal fluid calcium however, remained unchanged. At the beginning of the study, the spinal fluid calcium was 3.9 mg., the total calcium 5.4 mg., and the filterable calcium 2.3 mg. With therapy the total rose to 9.2 mg., the filterable rose to 5.5 mg., and the spinal fluid calcium remained at 3.9 mg.

The results in these cases (O. C. and C. E.) indicate that it is

principally the filterable calcium of the serum which falls in parathyroid tetany. This agrees with the results of Gunther and Greenberg.[5] It is not in agreement, however, with the observations of Cameron and Moorhouse,[10] who reported that the non-filterable calcium of serum almost disappeared in parathyroid tetany in dogs. The last named investigators used the spinal fluid calcium as a measure of the filterable calcium of serum.

Summary. Estimations of the total and filterable calcium of serum and the total calcium of the spinal fluid were made in 9 persons with normal calcium metabolism. A series of comparisons of the total and filterable calcium of serum with the total spinal fluid calcium was made in 2 cases of hyperparathyroidism and 2 cases of hypoparathyroidism. In each person with abnormal calcium metabolism the comparisons were repeated frequently at intervals of one to several days over an extended period of time. This was done in order to ascertain whether there might be daily variations in the relationship of the serum filterable calcium and spinal fluid calcium, and to be sure that any discrepancy between the two values was not due to failure of the two systems to reach equilibrium because of a time factor. The filterability of the spinal fluid calcium was also studied in subjects with normal and abnormal calcium metabolism.

Conclusions. 1. Filterable calcium of serum is elevated in hyperparathyroidism and lowered in hypoparathyroidism.

2. Filterable calcium of serum and total calcium of spinal fluid are usually practically equal over the normal range of serum calcium values. In 2 of 9 persons in our normal series, however, the filterable calcium of serum exceeded the total spinal fluid calcium by an amount greater than the usual experimental error.

3. The spinal fluid calcium was slightly elevated in 1 case of hyperparathyroidism and normal in another case. It was also normal in 2 cases of hypoparathyroidism.

4. Wide variations in filterable calcium of serum may occur without any change in the spinal fluid calcium. It is proper, therefore, to question all values for filterable serum calcium which are obtained by estimating the spinal fluid calcium.

5. The calcium of spinal fluid is completely filterable.

6. It was impossible to raise the total serum calcium above 7.6 mg. in 1 case of hypoparathyroidism by administering 4 cc. of parathyroid extract and 4 gm. of calcium lactate daily, but the symptoms and signs of tetany were completely relieved.

7. In 1 proved case of hyperparathyroidism, the maximal change in the serum calcium values occurred within 3 days after the removal of the parathyroid adenoma. This should be kept in mind in using the serum calcium as the criterion of success of surgical treatment of parathyroid adenomas.

8. Time was not the determining factor in the difference between the filterable serum and spinal fluid calcium in 4 patients with abnormal calcium metabolism.

9. The spinal fluid probably does not represent an ultrafiltrate of the plasma so far as calcium is concerned.

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CAUSES OF DEATH IN DIPHTHERIA AND THEIR PREVENTION.*

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One might properly suggest that the simplest manner for preventing deaths from diphtheria is through active immunization. We not merely agree that this is quite true but are willing to admit that it is the only certain method of eliminating fatalities from this infection. Nevertheless, just as smallpox has continued to exist

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and cause an unnecessary loss of life for the 139 years since the introduction of vaccination, so a somewhat similar situation may be expected in respect to diphtheria. Many parents will fail to protect their children by the means now available. It is among this portion of the population who contract diphtheria with which we are now concerned.

The causes of death from diphtheria fall into three classes: (1) asphyxia; (2) bronchopneumonia, and (3) myocarditis (toxemia).

The first group embraces those cases of diphtheria in which the membrane is located within or below the larynx. And a false membrane within or below the larynx does not necessarily signify an extension of the infection from above downward, for in the majority of laryngeal diphtheria patients there is no visible membrane outside the larynx. In reality, many cases of this kind develop by extension of the diphtheritic process from below upward. This fact has an important bearing on the treatment required.

In the average case of diphtheria, when the site of the membrane is in or below the larynx, toxemia is not the primary factor that endangers life. It is the membrane itself acting in a mechanical way that threatens asphyxiation by blocking the lower air passages. Consequently relief from this condition must be accomplished either by intubation or tracheotomy. Diphtheria antitoxin alone, regardless of dosage, will seldom suffice to save the patient. We have stated that usually the toxic action of diphtheritic infections in this group is not pronounced. As evidence of this, it is found that the complications associated with other forms of diphtheria rarely occur when the infection (membrane) is confined to the larynx or trachea. Myocarditis, albuminuria and the paralyses are notably absent.

Asphyxiation, then, as a cause of death in diphtheria must be prevented by surgical, not medical, treatment. Here diphtheria antitoxin is not the artillery: it is the infantry in the fight for life.

In the second class of causes of death from diphtheria, we must contend with bronchopneumonia. This is perhaps the most difficult onslaught to avoid, because there is no certain method of prevention. Nor is there any reasonably sure means of victory after bronchopneumonia is firmly entrenched. It is principally in laryngeal diphtheria that bronchopneumonia may intervene and snuff out a life after intubation or tracheotomy has saved the patient from asphyxiation. Aspiration pneumonia in intubated patients is not nearly as frequent as some would have us believe. It is always a possibility, nevertheless. With proper methods of feeding, however, it is not likely to occur. Clean hands and clean instruments when performing an intubation are vital necessities. With these simple requirements we found some years ago that the frequency of bronchopneumonia as a cause of death in diphtheria could be greatly diminished. The use of mechanical suction appa-

ratus and elevating the foot of the bed are also important assets in the avoidance of pneumonia in those patients who have profuse nasal or oral discharges.

In the third class of the causes of death in diphtheria we have the most important group. It holds this position not merely because it constitutes the greatest number of fatalities, but also on account of the possibilities of prevention, providing the signs of impending disaster are promptly recognized and immediate and appropriate action taken.

This is the group in which myocarditis so often plays the part of the executioner. However, the death sentence is not carried out with any undue haste. The limitation of life cannot be compared with the patient who suffers from laryngeal diphtheria when, within the space of a few seconds the possession of dexterity and experience, or lack of it, on the part of the physician, determines the outcome.

In pharyngeal or nasopharyngeal diphtheria, the absorption of toxin from the site of the membrane is rapid. Within 3 days of the onset of the disease, pronounced toxemia may be evident. Nevertheless, if treated with adequate doses of antitoxin within that period of time, comparatively few patients are lost. But when more than 3 days have elapsed prior to antitoxin treatment, the fatality figures mount by leaps and bounds, provided antitoxin alone is relied upon to preserve life. It is to such patients as these that we have directed particular attention during the past 2 years.

Diphtheria patients with a profound toxemia usually have a cervical adenitis, commonly described as the "bull neck type." The neck, however, does not have the hard brawny feeling that is sometimes encountered in scarlet fever. The tissues suggest that much of the swelling is due to edema. The patient is often not merely rational but very clear mentally. A profuse nasal discharge is likely, and a foul odor, sometimes referred to as typical of diphtheria, permeates the atmosphere about the patient. The finding of a marked albuminuria is very significant, for it indicates a bad prognosis. An enlarged and tender liver will also be noted in many such patients. The temperature means little, insofar as having any bearing on the true condition of the patient. It may be normal, slightly subnormal, or be elevated 3 to 4°. As a rule, the temperature ranges from 99 to 103° prior to antitoxin administration.

When one observes a patient such as described here, it is possible to foretell with a surprising degree of accuracy what may be expected and the approximate time when certain expectations will be fulfilled. After the administration of diphtheria antitoxin, the temperature will usually rise 2 or 3° during the next 12 to 24 hours. Within 48 hours after antitoxin injection, considerable improvement is often manifest and there are likely to be high hopes for recovery. During the next 2 or 3 days the membrane may have completely

disappeared and the pulse rate, which perhaps was 110 before antitoxin treatment, is now about 90. At this time, little or no abnormalities of the heart may be detected with the stethoscope, even in the hands of the heart specialist. However, from the 10th to the 12th day of the disease, which may be possibly 6 or 8 days after antitoxin has been given, a sharp drop in the pulse rate occurs. There is often a decline of 30 to 40 beats per minute within a space of a few hours. This is one of the commonest omens of impending danger, though the patient may have no complaint of ill feeling. However, within the next 12 to 24 hours, abdominal pain may occur, and if this is accompanied by vomiting, death is practically certain, and an autopsy establishes a diagnosis of acute myocarditis.

For a considerable number of years we have made such observations of diphtheria patients in the contagious disease hospitals. We have seen patients enter and found that we frequently could anticipate certain complications, basing our predictions on signs and symptoms present at that time. This has been particularly true in respect to myocarditis. When myocarditis did develop, we then made use of dextrose intravenously and this form of treatment seemed to be beneficial.

About a year ago,[1] we reviewed 496 cases of diphtheritic myocarditis, and undertook to emphasize the value of dextrose intravenously in the treatment of such cases. Our customary practice had been similar to that of others[2] who had used glucose intravenously in the treatment of diphtheritic myocarditis. We began the administration of glucose as soon as myocarditis was diagnosed. Yet in many instances we felt we knew several days in advance that the patients would have myocarditis. When the administration of glucose was withheld until a definite diagnosis of myocarditis was made, comparatively few such patients survived. Therefore, early in 1934, it was decided that certain classes of diphtheria patients would be placed on glucose therapy as soon as admitted to hospital, and a definite plan was adopted for both the Municipal Contagious and Cook County Contagious Disease Hospitals. Intravenous glucose was ordered as routine treatment for all diphtheria patients coming within any of the following groups: (1) those ill more than 3 days prior to receiving antitoxin; (2) "bull neck" types, irrespective of the day in the course of the disease that antitoxin was injected; (3) patients with marked albuminuria; (4) all postnasal cases and all malignant types of any character.

Patients classified according to any of the foregoing groups were placed on the critical list when admitted to the hospital. Glucose—10% in double distilled water—was administered at once by the gravity method. The quantity usually varied from 500 cc. for a child, to 1000 cc. for an adult, but was also determined to some extent by the condition of the patient. This treatment was repeated daily for a minimum period of 8 days, which frequently carried the

patient through the precarious stage (10th to 12th day of disease) during which diphtheritic myocarditis so frequently manifests itself.

In one instance, a woman, aged 39, receiving daily treatments was given 13,365 cc. of 10% glucose solution, or 1365 gm. of glucose, within 37 days.

Among 225 diphtheria patients admitted to the Municipal Contagious Disease Hospital in 1934, there were 83 classified as critical when they entered. Nearly all of these 83 were of a type usually described as malignant. However, we believed the severity of their infections in most instances should be attributed to delay in antitoxin administration rather than to some extreme virulence of the diphtheria bacillus. Many of these patients had been ill from 5 to 7 days before coming to the hospital. For the entire group of critical cases, the average duration of illness prior to antitoxin administration was 4.85. Hottinger[3] reported a fatality rate for malignant diphtheria in Düsseldorf of from 50 to 60%.

In our group of 83 critical diphtheria patients, the average number of days for glucose administration was 9, and the average total dose of 10% glucose solution, 3492 cc. Among these 83 patients there were but 10 deaths. Thus, the fatality rate was only 12% in contrast to a rate of from 30 to 60%, which would ordinarily be expected without glucose. Moreover, it seems worthy of mention that of the 10 deaths, 1 occurred in less than 1 hour after admission to the hospital, and another of the fatalities took place in less than 24 hours after admission. With the exclusion of these 2 deaths, we find that 81 so-called malignant cases of diphtheria that were placed on glucose therapy, had a recovery rate of more than 90%. Or in other words, the fatality rate was 9.8%, a figure that might not be regarded with disfavor for the average hospital cases of diphtheria. Nevertheless, the 83 patients treated with glucose were in desperate condition. In this connection it is rather interesting to find that the average dose of diphtheria antitoxin for the patients in this group was only 39,500 units. This fact, together with the successful results of treatment, seem to further justify our conclusions reached some years ago that massive doses of diphtheria antitoxin are neither necessary nor of value in saving lives when there has been unusual delay in serum administration.

Very recently, Darrow and Yannet[4] reported on the use of glucose in malignant diphtheria. In a group of 5 cases they had 4 recoveries and 1 death. These authors point out that diphtheritic intoxication produces extensive derangement of carbohydrate metabolism, and they further state there is hepatic insufficiency, renal insufficiency and shock. In reporting their clinical experience, it seems to me, however, that the mode of treatment adopted was much the same as used by others in the past. Glucose was given the patient in order to combat degenerative changes in the tissues after symptoms of such changes had become plainly evident. To be of most value,

glucose should be administered without waiting for physical signs of myocarditis.

Summary. 1. When the diphtheria membrane is located within or below the larynx, diphtheria antitoxin alone will seldom save the patient. Usually intubation or tracheotomy is required.

2. Although there is no absolute method for preventing bronchopneumonia in diphtheria, the frequency of this complication can be held to a minimum if minute attention is paid to cleanliness of hands and instruments when performing intubations, and if correct methods of feeding are followed for patients wearing intubation tubes.

3. Diphtheritic myocarditis can often be prevented by the use of 10% dextrose solution intravenously, provided this treatment is begun sufficiently early and continued daily for a sufficient length of time.

Dextrose helps to maintain the general nutrition of the patient who may be unable to swallow or retain food. In addition, it seems to provide nourishment to the heart muscle, and thus lessen passive congestion of the liver. The necessity for immediate institution of glucose therapy increases according to the number of elapsed days prior to antitoxin injection.

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BOOK REVIEWS AND NOTICES

DISEASES OF THE NERVOUS SYSTEM. A Text-book of Neurology and Psychiatry. By SMITH ELY JELLIFFE, M.D., PH.D., Formerly Professor of Psychiatry, Fordham University, and Adjunct Professor of Diseases of the Mind and Nervous System, New York Post-Graduate Medical School and Hospital, and WILLIAM A. WHITE, M.D., Superintendent of St. Elizabeth's Hospital, Washington, D. C.; Professor of Psychiatry, George Washington University, etc. Pp. 1175; 497 illustrations and 13 plates. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $9.50.

"IN the preparation of this edition the authors have undertaken to include as far as possible all important contributions which have sufficient weight and have been made since the last edition. The whole book has been carefully revised, some portions rewritten and many additions have been made to the text. That it has kept within the same number of pages as the last edition is due to the fact that the pages throughout have been enlarged so that the bulk of the book might not be increased materially. To be somewhat specific as to the nature of the new material, briefly it may be said that new methods of examination have been added; the chapter on the vegetative nervous system brought into line with present-day investigations, particularly the pathways of the hypothalamic region presented in the light of recent metabolic studies; the newer surgery of the sympathetics has been discussed and reserved judgments expressed. The endocrinopathies, especially the pituitary sections, have been rewritten. In the sensorimotor neurology, especially of the peripheral systems, little of signal importance has been produced since the last edition. The newer work on spinal cord lesions, especially the encephalomyelitides, has been carefully revised. Rarer peduncular and mid-brain lesions have been included and likewise certain new issues in the discussion of the localization of brain tumors. In the final section, on the symbolic systems, much new material has been added, particularly of an interpretative character, and especially material which tends to illustrate the distinction between those common possessions of man which have been laid down in well defined structuralizations and those more or less incidental results of his individual experiences during his lifetime. Especial attention is called to our effort in the full citation of the significant literature to indicate the historical developments in the knowledge of the various matters discussed." (From the Authors' Preface.)

THE PATHOLOGY OF INTERNAL DISEASES. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.); Dipl. Psych., F.R.S. (CAN.), Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital. Pp. 904; 335 illustrations. Second edition. Philadelphia: Lea & Febiger, 1935. Price, $10.00.

THE first edition of Professor Boyd's book was reviewed in this Journal (181, 419, 1931). In this revised edition much of the book has been rewritten and a considerable amount of new material has been added. Every chapter bears witness to the successful accomplishment of the aim stated "to develop the subject along clinical and physiological lines." Stress has

been laid on relating structural changes to functional disturbances, symptoms to lesions. The introduction of a number of pictures of clinical conditions serves to emphasize this viewpoint. From the opening sentence ("Of all the ailments which may blow out life's little candle, heart disease is the chief") to the last page, the book is well written; it is also very readable, and not the least so because of the many apt quotations, some but a phrase or a line, from the original descriptions of lesions and symptoms by the masters.

As the title states, the book deals with the pathology of internal diseases, including those of the nervous system. The student in his preclinical as well as in the clinical years will find it an excellent aid for linking the pathologic laboratory to the ward; to the practitioner it will bring a thoroughly satisfactory and modern presentation of the science of internal diseases. B. L.

A Textbook of General Bacteriology. By Edwin O. Jordan, Ph.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Pp. 825; 202 illustrations. Eleventh edition, entirely reset. Philadelphia: W. B. Saunders Company, 1935. Price, $6.00.

"The current—one might say torrent—of investigation has run strong since the tenth edition of this book was printed, and signal advances have been made in our knowledge. It has been necessary to rewrite many portions and to add materially to others. The important topic of bacterial variation is dealt with in a new and separate chapter; the chapters on Immunity, on Streptococci, on Salmonella, on Brucella, on Rickettsia and on Spirochetes have received many modifications and additions; and the section on The Viruses and Virus Diseases has been largely rewritten. In an attempt to promote grouping by natural relationships a few changes have been made in the arrangement of chapters. The most important of these has been to bring together the Actinomycetales: The diphtheria bacillus, the tubercle bacillus, the actinomyces, etc.

The problem of nomenclature, always in bacteriology a vexed and difficult one for both student and teacher, is treated in what some bacteriologists will consider too conservative a manner. The names for bacteria, however, used by many recent writers, notably by the authors of the admirable nine-volume System of Bacteriology published by the British Medical Research Council, is additional evidence of the impossibility of achieving a unified nomenclature except by international agreement. For the present we may well hesitate to use in a textbook names that have not won pretty general acceptance." (From the Author's Preface.)

A Textbook of Laboratory Diagnosis. With Clinical Applications for Practitioners and Students. By Edwin E. Osgood, M.A., M.D., Assistant Professor of Medicine and Biochemistry, Director of Laboratories, University of Oregon, School of Medicine, Portland. Pp. 585; 27 illustrations and 10 colored plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, $6.00.

"Among the major additions from the work of other investigators are the technic and interpretation of the blood urea clearance test, insulin coefficient, the blood bromide determination, the Friedman test, the galactose tolerance test, the Paul and Bunnell test for heterophile antibodies, also the technic for the quantitative determination of plasma proteins, proteins in cerebrospinal fluid and other body fluids, and the forensic

applications of blood grouping. Among the major additions from the original investigations of the author and his co-workers are new data on the normal values for plasma proteins, for the renal threshold, for the erythrocyte count, hemoglobin, cell volume, color, volume and saturation indexes, total and differential leukocyte counts, sedimentation rates, reticulocyte count and sternal marrow. The improved technic for reticulocyte counting, methods for accurate prognosis from changes in neutrophil morphology and a simple clinical method for obtaining sternal marrow during life are further additions. New data on the histogenesis of the monocyte and plasma cell derived from a study of monocytic and plasma cell leukemias are also included from our work. Special attention has been given both in the text and in the Index by Diseases to the new development in the diagnosis of such conditions as hyperinsulinism, hyperparathyroidism, infectious mononucleosis, erythroleukoblastosis, teratoma testis, iron deficiency anemias, etc." (From the Author's Preface.)

DISEASES OF THE THYROID GLAND. By ARTHUR E. HERTZLER, M.D., Chief Surgeon, Halstead Hospital; Professor of Surgery, University of Kansas. With a Chapter on Hospital Management of Goiter Patients by VICTOR E. CHESKY, M.D., Chief Resident Surgeon, Halstead Hospital. Pp. 348; 181 illustrations. Third edition, entirely rewritten. St. Louis: The C. V. Mosby Company, 1935. Price, $7.50.

IN this, as in previous editions, the author presents the results of his personal experience with thyroid disease, and his highly individual opinions (often unique) concerning its clinical and pathologic aspects. No attempt is made to reflect generally prevailing views of the subject. There is little reference to the literature and no bibliography; there is occasional evidence of careless writing. The increasing importance of the endocrine interrelationships of the thyroid is practically ignored. The classification of goiter (of which too many already exist) is vague and confusing, and many of the illustrations are of little value. The drawings illustrating surgical anatomy and technique are good. The book is not a valuable contribution to the literature of thyroid disease. E. R.

DISORDERS OF THE BLOOD. Diagnosis, Pathology, Treatment and Technique. By LIONEL E. H. WHITBY, C.V.O., M.C., M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), D.P.H., Assistant Pathologist, the Bland-Sutton Institute of Pathology, The Middlesex Hospital, and Pathologist, The Children's Hospital, Hampstead, and C. J. C. BRITTON, M.D. (NEW ZEALAND), Assistant Pathologist, The Christchurch Hospital, New Zealand; Late Postgraduate New Zealand Scholar, The Middlesex Hospital, and Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital. Pp. 543; 53 illustrations and 12 plates (8 in colors). Philadelphia: P. Blakiston's Son & Co., Inc., 1935. Price, $7.00.

IN few fields of clinical medicine have the accumulation of new facts and the comprehension of disease pictures increased more rapidly in recent years than in hematology. This has naturally been reflected in the number of new books that have appeared on the blood and its disorders, one of the best being this latest contribution to the subject from the Middlesex Hospital. The extensive hematologic literature of the past decade—especially in England, Germany and this country—has been thoroughly and discriminately covered, to produce a work that covers not only the outlines of normal and pathologic hemolytopoiesis but also the various disorders of

the blood, their nature, diagnoses and treatment. Especially are the more recent advances comprehensively and comprehendingly presented. On many undecided points the prevalent view is the one regularly presented, but attention is as regularly called to the minority standpoint. A convenient novelty is the insertion of Summaries at the ends of most of the chapters. A final chapter (52 pages) on technique includes determinations of blood volume, grouping, spectroscopy, bone-marrow biopsy, as well as the usual hematologic methods. E. K.

ARCHIVOS DE MEDICINA LEGAL E IDENTIFICAÇÃO. Official Publication of the Institute of Identification. Edited by LEONIDIO RIBEIRO, M.D., Director of the Institute of Identification. Vol. V, No. 11. Pp. 212; illustrated. Rio de Janeiro: Imprensa Nacional, 1935. (No price given.)

ONE of the outstanding institutions in the field of criminology from the medical standpoint is the Institute of Identification in Rio de Janeiro. Its eminence is largely due to its organizer and director, Dr. Ribeiro, who in 1933 was awarded the Lombroso Prize by the Royal Academy of Medicine in Rome. The contents of this issue of the Archives of Legal Medicine and Identification pay high tribute to the excellent investigative and educational work being carried on in the Institute. Of particular interest is Dr. Ribeiro's article on the "Ability of Leprosy to Alter the Designs of Finger Prints." R. K.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. EIGHTH SESSION. Herausgegeben von PROF. DR. EB. KOCH, Bad Nauheim. Pp. 262; 80 illustrations. Leipzig: Theodor Steinkopff, 1935. Price, Rm. 15.

FOR this eighth annual session, held at Wiesbaden, the main topic of "Circulation and Respiration" was selected. The three chief articles are by Hess, of Zurich, on the Physiologic Interplay of Circulation and Respiration; by Wenckebach, of Vienna, on Disturbances of Respiration and Their Influence on the Circulation; and by Hochrein, of Leipzig, on the Pulmonary Circulation Under Normal and Pathologic Conditions. Other well-known authors are among the 35 contributors to the program, the last 11 items of which are on miscellaneous topics. The general level of excellence appears to be up to former standards. E. K.

FOOD AND BEVERAGE ANALYSIS. By MILTON A. BRIDGES, B.S., M.D., F.A.C.P., Director of Medicine, Department of Correction Hospitals, New York; Consulting Physician, Seaview Hospital, Staten Island; Clinical Professor of Medicine and Lecturer in Therapeutics, New York Post-Graduate Medical School, Columbia University, etc. Pp: 246. Philadelphia: Lea & Febiger, 1935. Price, $3.50.

OVER 3200 analyses of nutritive values, over 400 iodin analyses, 350 analyses of vitamins and the analyses of over 500 foods for their content of various minerals make this little volume the outstanding publication in its field. Noteworthy is the inclusion of numerous analyses of canned and packaged, *i. e.*, commercial foods, thereby greatly enhancing the practical value of the information. The data are conveniently presented in tables, with alphabetical listing of foods and with not only the percentage compo-

sition of the nutritive elements but also the number of grams of each element in a specific portion (based on household measure) of the food. The book will prove valuable to everyone who deals with any phase of practical dietetics. R. K.

A TEXT-BOOK OF FRACTURES AND DISLOCATIONS. Covering Their Pathology, Diagnosis and Treatment. By KELLOGG SPEED, S.B., M.D., F.A.C.S., Professor of Clinical Surgery, Rush Medical College of the University of Chicago; Attending Surgeon, Presbyterian Hospital, etc. Pp. 1000; 1042 illustrations. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $11.00.

THIS third edition of Speed's excellent book on fractures and dislocations is welcomed by those practitioners and surgeons who treat fractures. The plan of the original edition has been preserved. Each fracture is treated as a complete unit, with a description of the anatomy, the cause and incidence of the fracture, pathology, complications, symptoms and diagnosis, and then a full discussion of the standard methods of treatment. The methods suggested are not always the most advanced, but they are those which have been tried and proved useful in an extensive fracture experience. At the end of each section there has been appended in this edition a list of references for the use of students and surgeons who wish to investigate the literature further. The illustrations are in many cases excellent actual photographs or tracings from roentgenographs. The work will be found to be an indispensable standard reference for surgeons and students.

L. F.

PRECIS DE PATHOLOGIE EXTERNE. In 2 volumes. By PROFESSOR E. FERGUE. 9th edition. Pp. 2370; 1164 illustrations and 4 plates. Paris: Gaston Doin & Cie. Price, paper, 180 francs.

THIS precis, awarded the Godard prize by the Academie de Médecine in 1903, now appears in its ninth edition. The author has brought together material seldom if ever presented in an American or English text of comparable length. Though a counterpart of our textbooks of surgery, it presents pathologic processes, particularly the common surgical conditions, from the viewpoint of the preclinical sciences. To this is added an excellent presentation of symptomatology and diagnosis. Treatment is outlined briefly, though the paragraphs devoted to it are more suitable as references than as descriptions. The emphasis is distinctly French and in many instances is quite different from that of English and American authors.

J. R.

VIER VORLESUNGEN ÜBER KREISLAUFFRAGEN. Gehalten an der Spanischen Universidad International de Verano en Santander. By DR. BRUNO KISCH, ordentlicher Professor der Physiologie an der Universität Köln. Pp. 64; 6 illustrations. Köln: Paul Kuschbert, 1934. Price, Rm. 3.60.

THESE lectures given in the Casa de Salud at Santander deal with rather specialized recent fields of cardiac functional pathology, chiefly with the humoral changes in the blood in heart disease. In the first, on "Circulation and Metabolism," the lecturer considers how the circulation and the blood content change in various normal conditions and in heart disease and how this in turn affects the heart and the other viscera. In the second lecture on "Humoral Blood Changes in Circulatory Insufficiency," the importance of the circulation in regulating bodily activity is stressed. "The Circulation and the Autonomic Nervous System" (third lecture)

offers numerous examples of the importance in the economy of the organism of the "life nerves," which in vital organs are always beyond voluntary control. In the last lecture, on "The Irradiation of Autonomic Reflexes," is expounded the author's law: "In the domain of the automonic nervous system . . . reflexes (exclusive of axone reflexes) are never limited to a single reflex zone." These lectures should be of interest and value especially to those concerned with the special field that they cover. E. K.

ARTHRITIS AND RHEUMATOID CONDITIONS. Their Nature and Treatment. By RALPH PEMBERTON, M.S., M.D., F.A.C.P., Professor of Medicine in the Graduate School of Medicine, University of Pennsylvania; Physician to the Abington Memorial and Bryn Mawr Hospitals, etc. Pp. 455; 69 illustrations, 60 tables and a colored plate. Second edition, thoroughly revised. French translation of first edition, 1933. Philadelphia: Lea & Febiger, 1935. Price, $5.50.

THE reader will find here an authoritative and complete statement of our present knowledge on the subject, a knowledge to which the author, in upwards of 20 years of study of this disease, has made valuable contributions. The appearance of this second edition, as well as a translation of the first into French, bear witness to the deserved popularity of the work. R. K.

A MARRIAGE MANUAL. A Practical Guide-Book to Sex and Marriage. By HANNAH M. STONE, M.D., Medical Director of the Birth Control Clinical Research Bureau and of the Marriage Consultation Centers at the Community Church and Labor Temple, New York, and ABRAHAM STONE, M.D., Adjunct Urologist at the Sydenham Hospital; Co-Director of the Marriage Consultation Centers at the Community Church and Labor Temple, New York. Pp. 334; 8 illustrations. New York: Simon and Schuster, 1935. Price, $2.50.

THE book fully lives up to its subtitle: it is practical, accurate and instructive. Emphasis and clarity have been heightened by the form of presentation: questions and answers between a young couple and the physician. Doctors will find this an excellent book to recommend to their patients. R. K.

THE DISEASES OF THE ENDOCRINE GLANDS. By HERMANN ZONDEK, M.D. (BERLIN), Director of the Medical Division, Bikur Cholim Hospital, Jerusalem, etc. Pp. 492; 168 illustrations. Third edition, revised and enlarged. Translated by CARL PRAUSNITZ, M.D. (BRESLAU), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Honorary Research Fellow, Victoria University of Manchester, etc. Baltimore: William Wood & Co., 1935. Price, $11.00.

THIS book cannot be recommended as it is full of speculative and unsound conceptions and unwise therapeutic recommendations.

A few examples speak for themselves: Osteomalacia, instead of being accepted as essentially due to deficiency in vitamin D, is regarded by the author as an endocrine disorder. He believes that excessive parathyroid function can produce osteomalacia "either directly or indirectly through the medium of the ovaries" (p. 357), and that severe cases of osteomalacia require surgical removal of the ovaries. Fortunately, however, he advises vitamin D administration, but explains that "the action of vitamin D is known to resemble that of parathormone in many respects,

especially as regards calcium metabolism" (p. 360). Although there is good evidence that generalized osteitis fibrosa is due to excess parathyroid function, the author advises treating this condition with parathormone "in order to stimulate production of osteoblasts and formation of new tissues," and yet also advises what others advocate, removal of a parathyroid tumor if it is present.

He states: "The ultimate reason for the enhanced metabolism in Graves' disease must be referred to constitutional peculiarities of the tissues, chiefly the muscles" (p. 136). He believes in a "peripheral" origin of Graves' disease due to disturbances in "ionic balance in and around cells" of muscles and other tissues which are "constitutionally supersensitive to thyroid hormone." For Graves' disease, he has found beneficial in some cases pituitrin, insulin, liver extract, vitamin A to restore the disordered liver function, and calcium, in addition to the more conventional treatment.

"Occasionally it is necessary to attune the tissues to the hormone by altering their physicochemical conditions. This may be done, *inter alia*, by spa treatment (*e. g.*, Karlsbad, Marienbad, Vichy), by diet, and protein therapy" (p. 106).

He recommends administering tuberculin in Addison's disease due to tuberculosis. He has used insulin in Simmonds' disease, although we know that such patients are likely to have spontaneous hypoglycemia. He believes he is giving anterior pituitary hormones when he is giving prolan.

"Hæmatopoiesis and the distribution of the blood within the body are regulated essentially by the thyroid hormone. The hormone evidently influences the complex system regulating the composition of the blood, *viz.* bone marrow, spleen, liver, etc." (p. 39). I. Z.

SYPHILIS, IHR BIOLOGISCHER URSPRUNG UND DER WEG ZU IHRER AUSROTTUNG. By DR. MED. FERDINAND THUGUT. Pp. 109. Stuttgart: FERDINAND ENKE, 1931. Price, Rm. 4.00.

THE brochure, "Die Weltgeissel Syphilis," which appeared in 1926, proposed an ingenious theory of the origin of syphilis on the basis of recent studies on the mutability and changing virulence of the Spirochæta pallida. The author accepts the scarcely tenable view that syphilis, as we know it now, did not exist either in Europe or America before Columbus' time. It is possible, according to him, that the ancestor of the Spirochæta pallida, a harmless organism, was rendered highly pathogenic as a result of passage through new hosts. The eradication of syphilis according to the author depends on early diagnosis and treatment as well as individual prophylaxis. Written in a rather literary style this work makes interesting if difficult reading. J. S.

THE THEORY AND PRACTICE OF ANAESTHESIA. By M. D. NOSWORTHY, M.A., M.D., B.CH. (CANTAB.), Anesthetist to Westminister Hospital and Grosvenor Hospital for Women, etc. With a Foreword by I. W. MAGILL, M.B., B.CH. (BELFAST), Senior Anesthetist to Westminister Hospital, etc. Pp. 223; 35 illustrations. London: Hutchinson & Co., Ltd., 1935. Price, 12/6.

THIS small book gives the anesthesia essentials which the author has found valuable in teaching. Short chapters on the physiology of anesthesia precede chapters on anesthesia proper. Ether, chloroform, ethyl chlorid and nitrous oxid are discussed separately. The difficulties and dangers of anesthetic administration are pointed out and the author describes his methods for avoiding them. Short reference is made to the newer general

anesthetics: ethylene, cyclopropane and vinethene. Endotracheal anesthesia is described in detail. The discussion of spinal anesthesia (percain and stovain) is interesting to American surgeons. A chapter on the choice of anesthetic agents deals largely with the choice of the anesthetic in relation to the operation, rather than the choice in relation to the patient.

The book is too small to be considered anything more than a handbook for use in teaching anesthesia to beginners. The ideas expressed are largely those of the English viewpoint, which differ in many particulars from those in common usage in America. L. F.

ANEMIAS Y ALIMENTACIÓN. The Anti-anemic Principle of Liver and the Qualitative Factors of Foods (Vitamins, Ammo Acids, Iron and Copper). By JOSÉ SANCHEZ RODRIGUEZ, M.D. With a Foreword by PROF. GREGORIO MARANÓN. (Doctorate thesis, awarded the prize by the National Academy of Medicine, Spain, in 1935.) Pp. 165; 22 illustrations. Madrid: Ediciones del Arbol, 1935. Price, 12 pesetas.

THE author first reviews the development of our knowledge of the nature and causation of the anemias. He emphasizes that a proper conception of the subject must be based on an understanding of the biochemistry of erythropoiesis, and offers a physiopathologic classification of the anemias. Turning then to a consideration of pernicious anemia, he takes up as his major problem an investigation of the nature of the antianemic factor of a concentrated and purified liver extract for parenteral administration. He concludes that his extract does not contain iron, copper, the hematopoietic amino acids, the fat-soluble vitamins A, D and E, the water-soluble vitamins B_2 and C (thus differing with Castle and others who sought to identify the antianemic factor with B_2). It does contain the antineuritic vitamin B_1 in large amounts, but the failure of B_1 to cure pernicious anemia precludes it from being the antianemic factor. The author, therefore, concludes that one has to do with a new "antianemic vitamin," derivable probably from various sources and stored in the liver. The work should be of great interest to hematologists.

R. K.

METHODS AND MATERIALS OF HEALTH EDUCATION. By JESSE FEIRING WILLIAMS, M.D., Teachers' College, Columbia University, and FANNIE B. SHAW, M.A., University of Florida. Pp. 331; illustrated. New York: Thomas Nelson & Sons, 1935. Price, $1.65.

IN addition to the methods and materials of health education, the authors also discuss the philosophy of education in the light of the newer concepts of the child. Considerable space is devoted to the definition of terms in order to dispel the confusion wrought in the past by ambiguous or loose terminology in this field. Many of the older criteria of health, such as the height-weight standards, are dismissed and more adequate tests suggested. Many data and references are given to help the teacher to a clearer understanding of the physiologic and psychologic background of health and disease in the child. Several chapters on the problems of health in the school give an outline of the measures required for healthful school living. The final chapter is devoted to the health of the teacher. While some important subjects are dismissed with mere mention, the authors usually refer to publications where further details can be found. The problems of sex in relation to health education are not mentioned, and mental hygiene is discussed in one paragraph. However, the book should be of value to those interested in the education of youth. S. H.

DISEASES OF THE SKIN. By FRANK CROZER KNOWLES, M.D., Professor of Dermatology, Jefferson Medical College; Dermatologist to the Jefferson, the Pennsylvania, the Presbyterian and the Babies' Hospitals, etc. Pp. 640; 240 illustrations and 11 plates. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1935. Price, $6.50.

THERE are several highly original features about this third edition which give it distinction among most American texts on dermatology. First, the large section devoted to general dermatology, of which 35 pages are devoted to treatment. This section also includes such newer subjects in pathology as blood grouping, the endocrines, red cell sedimentation tests and clinical spectroscopy. Another distinctive feature is the freshness of the subject matter throughout the book, including such new and well-established entities as erythroplasis, tularemia, Habermann's syndrome, carotinoid pigmentation, necrobiosis lipoidica diabeticorum, ninth day erythema and the Senear-Usher syndrome. Corollary to this is the freshness of the references to the literature in which those dated 1935 are conspicuous. Illustrations are abundant and uniformly good. It is an ideal text for the medical student and the busy practitioner of general medicine.

F. W.

CLINICAL DIAGNOSIS BY LABORATORY METHODS. A Working Manual of Clinical Pathology. By JAMES CAMPBELL TODD, PH.B., M.D., Late Professor of Clinical Pathology, University of Colorado, School of Medicine, and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation); Head of Section on Clinical Laboratories, Mayo Clinic. Pp. 792; 370 illustrations, 29 in colors. Eighth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1935. Price, $6.00.

THE 8 editions that this book has achieved in 27 years are adequate evidence for the leading position that it has assumed in the field of clinical diagnosis. One of the most active specialties in medicine, it is constantly producing new methods and utilizing advances in borderline subjects, and has even reached the position where its best practitioners must frequently urge caution in attaching too much importance to laboratory methods. It is no small praise to say that this edition has successfully kept abreast with these advances.

E. K.

DIE WERKE DES HIPPOKRATES. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von PROF. DR. GEORG STRICKER, Würburg. Book 11 (price, Rm. 8; pp. 103): Die Epidemischen Krankheiten (Die Volkskrankheiten) (The Epidemic Diseases (Diseases of the People)), 1.–3. Book. Book 12 (price, Rm. 9.50; pp. 135): Die Epidemischen Krankheiten (Die Volkskrankheiten) (The Epidemic Diseases (Diseases of the People)), 4.–7. Book. Stuttgart: Hippokrates Verlag G.M.B.H., 1934. (To be published in 25 parts, costing *ca.* Rm. 100, card binding.)

THESE two sections include in 7 books the notes on epidemic diseases which Hippocrates prepared toward a treatise on epidemiology. They may be regarded as successors to his work on public hygiene, "Air, Waters and Places" (Part 6 of this collection). It seems that in long visits to various islands and coastal towns of the Ægean Sea where he was favorably received, Hippocrates and his retinue of students made copious notes on "wax tablets and leather sheets." These about 323 B.C. reached the library at Alexandria from which copies soon penetrated throughout the civilized world. As examples of the contents, in the first book the "constitutions" and diseases of the town of Thasos are described in successive years, with

a section on 16 clinical histories; in the second, the diseases of Kranon and Perinthos are considered from both the individual and epidemiologic standpoint, while the third is a collection of 12 case histories, and so on through four more books. In spite of the unedited, rough character of the notes (especially in the fifth and seventh book)—sometimes even composed of ungrammatical sentences, as the translator and annotator, Stricker, points out—the disease pictures stand out so sharply that they can almost without exception be identified today. Littré's text has been followed in the translation, with modifications as suggested by the studies of Ilberg and Kuhlewein, Wenkebach, and Rudolf Herzog. E. K.

NEW BOOKS.

The Cerebrospinal Fluid and Its Relation to the Blood. A Physiological and Clinical Study. By SOLOMON KATZENELBOGEN, M.D., Associate in Psychiatry, in charge of The Laboratory of Internal Medicine, The Henry Phipps Psychiatric Clinic, The Johns Hopkins Medical School, etc. Pp. 468; 48 tables and 20 charts. Baltimore: The Johns Hopkins Press, 1935. Price, $5.00.

The Parathyroids in Health and in Disease. By DAVID H. SHELLING, B.Sc., M.D., The Johns Hopkins University and Hospital, Baltimore. Pp. 335; 26 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, $5.00.

New Pathways for Children with Cerebral Palsy. By GLADYS GAGE ROGERS, Director of Robin Hood's Barn, A Camp School for Children with Cerebral Palsy, and LEAH C. THOMAS, Director of Therapeutics at Robin Hood's Barn, etc. With Photographs by NEWELL GREEN. Pp. 167; 12 illustrations. New York: The Macmillan Company, 1935. Price, $2.50.

Modern Office and General Practice. A Handbook of Practical Medicine. By DEANE R. BRENGLE, M.D. Pp. 320; illustrated. Kingsport, Tenn.: Southern Publishers, Inc., 1935. Price, $3.25.

Immunology. By NOBLE PIERCE SHERWOOD, PH.D., M.D., Professor of Bacteriology, University of Kansas, and Pathologist to the Lawrence Memorial Hospital, Lawrence, Kans. Pp. 608; 27 illustrations, 8 colored plates, and many tables. St. Louis: The C. V. Mosby Company, 1935. Price, $6.00.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. Eighth Session. Herausgegeben von PROF. DR. EB. KOCH, Bad Nauheim. Pp. 262; 80 illustrations. Leipzig: Theodor Steinkopff, 1935. Price, Rm. 15. (Review p. 280.)

International Clinics. Vol. IV, Forty-fifth Series, December, 1935. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 331; illustrated; 2 colored plates. Philadelphia: J. B. Lippincott Company, 1935.

The Patient and the Weather. Vol. I, Part 1, The Footprint of Asclepius. By WILLIAM F. PETERSEN, M.D. Pp. 127, lithographed; 94 illustrations. Ann Arbor: Edwards Brothers, Inc., 1935. Price, $3.75.

Klinik und Therapie der allergischen Krankheiten. By DR. ERICH URBACH, Privatdozent für Dermatologie an der Universität Wien; I. Assistant der Universitätsklinik für Geschlechts- und Hautkrankheiten in Wien (Vorstand PROF. DR. W. KERL). Pp. 781; 302 illustrations (26 in colors) and 24 tables. Wien: Wilhelm Maudrich, 1935. Price, Rm. 30.

Pollen Grains. Their Structure, Identification and Significance in Science and Medicine. By R. P. WODEHOUSE, PH.D., Scientific Director of the Hayfever Laboratory, The Arlington Chemical Company, Yonkers, N. Y. Pp. 574; 123 illustrations, 14 plates. New York: McGraw-Hill Book Company, Inc., 1935. Price, $6.00.

Données anatomiques en vue de la chirurgie réparatrice mammaire. By DR. CLAOUÉ et I. BERNARD. Pp. 58; 36 illustrations. Paris: Librairie Maloine, 1935. (No price given.)

Der Geburtstod (Mutter und Kind). By DR. SIGISMUND PELLER. Pp. 110; 56 tables. Wien: Franz Deuticke, 1936. Price, M. 5.

Royat Treatment in Cardiovascular Disease. By PIERRE NOËL DESCHAMPS, M.D. (Paris), Assistant Physician in Charge of the Cardiological Department, Lariboisière Hospital, Paris. Pp. 108. Baltimore: William Wood & Co., 1935. Price, $2.00.

The object of this book "is to make known to the English-speaking medical public the benefits to be derived from thermal carbon dioxide treatment," which seem to the author to be fundamental in the treatment of disturbances of the heart and vessels.

Hugh Owen Thomas. His Principles and Practice. By D. MCCRAE AITKEN, M.A., M.B., CH.B. (ED.), F.R.C.S. (ED. and ENG.), Director of Surgery, Robert Jones and Agnes Hunt Orthopædic Hospital; Senior Surgeon, St. Vincent's Orthopædic Hospital, etc. Pp. 96; 1 illustration and 8 plates. New York: Oxford University Press, 1935. Price, $4.25.

Autobiography Sigmund Freud. Translated by JAMES STRACHEY. Pp. 153; 1 illustration. New York: W. W. Norton & Co., Inc., 1935. Price, $2.00.

A Doctor's Odyssey. A Sentimental Record of LeRoy Crummer: Physician, Author, Bibliophile, Artist in Living, 1872–1934. By A. GAYLORD BEAMAN. With a word in Memory by A. EDWARD NEWTON and numerous memoirs and appreciations. Pp. 340; 21 illustrations. Baltimore: The Johns Hopkins Press, 1935. Price, $2.50.

NEW EDITIONS.

Principles of Bacteriology. By ARTHUR A. EISENBERG, A.B., M.D., Director of Laboratories, Sydenham Hospital, New York, and MABEL F. HUNTLY, R.N., M.A., Director of Nursing, Wesson Memorial Hospital, Springfield, Mass. With annotations and a section on Microbic Variations by F. E. COLLEN, M.S., PH.D., Professor of Bacteriology, Vocational School, Milwaukee. Pp. 378; 90 illustrations, and 8 colored plates. Sixth Edition. St. Louis: The C. V. Mosby Company, 1935. Price, $2.75.

Infant Nutrition. A Textbook of Infant Feeding for Students and Practitioners of Medicine. By WILLIAMS MCKIM MARRIOTT, B.S., M.D., Professor of Pediatrics, Washington University School of Medicine; Physician in Chief, St. Louis Children's Hospital. Pp. 431; 27 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, $4.50.

Diseases of Women. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Professor Emeritus of Clinical Gynecology, Washington University School of Medicine; Gynecologist to the Barnes Hospital, St. Louis Maternity Hospital, and St. Luke's Hospital, etc., and ROBERT JAMES CROSSEN, M.D., Instructor in Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Pp. 999; 1058 illustrations, including 1 colored plate. Eighth Edition, entirely revised and reset. St. Louis: The C. V. Mosby Company, 1935. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF
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SURGICAL DISEASES OF THE PANCREAS.

Not so many years ago the pancreas was thought to be practically unapproachable. Even as late as 1932, Heyn,[1] speaking of the treatment of hyperinsulinism, stated that the treatment was medical unless "increasing amounts of carbohydrate became necessary; then surgery, even if unsuccessful, must be tried" and that for the present "surgery appears not to be good enough." This attitude was not universal as evidenced by the striking results which we shall mention later, but there is rather generally still some apprehension regarding operative interference in diseases of the pancreas.

During the past decade there has been a renewed interest in the surgical approach to diseases of the pancreas. This has been chiefly concerned with the treatment of hyperinsulinism. The strikingly good results in the condition of patients from whom adenomata of the pancreas have been removed indicate the importance of this form of therapy. Whipple and Frantz[2] report 19 cases operated on by 10 different surgeons with no deaths, an indication that the mortality following this type of surgery need not be high.

One reason for the caution in attempting surgical treatment of pancreatic lesions lies in the anatomy and structure of this gland. Lying in the posterior portion of the abdomen in a retroperitoneal position, the pancreas is shielded from approach posteriorly by the great muscles of the back, the spine, the portal vein, the aorta, the left kidney and its vessels, and the pillars of the diaphragm. Thus it is seen that though the posterior surface of the pancreas is extraperitoneal it is inaccessible from the posterior approach because of these important structures. The anterior approach is complicated by

the depth of the organ, its position behind the stomach, and its close association with the duodenum and spleen.

The bloodvessels of the pancreas form a broad anastomosis, the branches of the celiac axis providing the major portion of the blood supply, the superior mesenteric supply the inferior pancreaticoduodenal and inferior pancreatic arteries. The gastroduodenal artery gives rise to the superior duodenal, the splenic artery to the superior pancreatic artery. The vessels form a circle about the pancreas. The blood supply of the pancreas is intimately associated with that of the duodenum, the stomach and the spleen. The veins of the pancreas empty into the portal, superior mesenteric and splenic veins, the drainage being finally into the liver through the portal vein. The distribution of the vessels of the pancreas has been studied recently by Wharton.[3]

In addition to studying the gross distribution of the vessels, Wharton studied the finer branches and anastomoses within the pancreatic tissue. The arterial plexus is formed from the circle of vessels supplying the gland, a single artery entering a lobule and dividing to form a glomerular-like structure of a sinusoidal nature among the cells of the islands of Langerhans. From these sinusoids small vessels pass into the interacinar capillary network. It can be seen from Wharton's[3] description that the blood stream widens markedly, so that the islands of Langerhans are bathed in a slow stream of blood. In addition to the clear description of his own studies, Wharton reviews and discusses the work of earlier investigators on the blood supply of the pancreas.

Besides the rich blood supply, another factor which commands gentleness of manipulation of the pancreas is its friable lobular structure. When torn across, the pancreas presents potentialities of drainage of material with a high enzymatic content which can cause liquefaction and fat necrosis of the surrounding tissues.

The external secretion of the pancreas, which is rich in digestive ferments, reaches the duodenum through the main duct, the duct of Wirsung, which traverses the entire length of the gland to join, as a rule, the common bile duct just proximal to the ampulla of Vater. Usually an accessory duct, the duct of Santorini, communicates with the main duct within the pancreas and empties into the duodenum at a point above the entrance of the main duct. There have been many variations noted in the ductal system of the pancreas. At times the accessory duct has no connection with the duodenum. When there is an obstruction at the ampulla of Vater the accessory duct may be the only functioning outlet and it is possible for all the external secretion to pass through it.

The lymphatic drainage of the pancreas, according to Bartels,[4] is into four groups of lymph nodes: 1, at the hilus of the spleen; 2, on the superior portion of the pancreas; 3, on the inferior surface of the pancreas; and 4, at the head of the pancreas. It is concerning this last group of nodes that much controversy has arisen with regard to the etiology of acute pancreatitis. It must be kept in mind that into these lymph nodes drain not only the pancreas but also the spleen, stomach, duodenum and hepatic structures.

The two surgical diseases of the pancreas most commonly met with

are carcinoma, usually situated at the head, and pancreatitis. About the etiology of acute pancreatitis much has been written. The occurrence of acute pancreatitis in association with gall bladder disease for many years suggested that possibly acute pancreatitis was the result of infection which had spread from the gall bladder to the pancreas through lymphatic channels. Deaver and Pfeiffer,[5] Sweet,[6] and Graham and Peterman[7] have presented evidence in its favor. Graham and Peterman injected bacteria into the portal vein and traced the infection from the liver to the gall bladder and thence by lymphatic extension to the nodes lying at the head of the pancreas. Inflammatory changes were also found in the pancreas. Kauffman[8] repeated some of the experiments of Graham and Peterman and confirmed the findings of lymphadenopathy in the nodes at the head of the pancreas but, except in cases where a blood stream infection or contact inflammation was present, found no evidence of pancreatitis. Kauffman argues that the lymphatic drainage is away from the area and the valves in the lymphatic channels would prevent backflow. His results would tend to deny the possibility of extension of infection in the gall bladder to the pancreas by lymphatic channels, a concept which has for many years been quite generally accepted. It is only the occasional case in which pancreatitis is found not associated with signs of inflammatory process in the gall bladder. Whether or not the extension of inflammation from the gall bladder to the pancreas by the lymphatics is the explanation of the etiology of acute pancreatitis, the association of inflammation in these two organs is too common to pass by without further proof that this theory is not tenable in some cases at least.

The close association of the common bile duct and duct of Wirsung suggests the possibility of the passage of bile into the pancreas when the ampulla of Vater is obstructed. Many attempts have been made to produce acute pancreatitis experimentally by injecting bile into the ducts. Opie[9] produced pancreatitis by the injection of bile into the pancreatic ducts, but it was necessary to inject as high as 5 cc., which is enough to cause distention of the ducts and so introduce an added factor of trauma. Pancreatitis has been produced by the injection of bile salts into the pancreatic duct but this is not wholly physiologic. Archibald[10] believes that it is the entrance of altered bile into the pancreatic ducts which produces the damage, normal bile causing but a transient edema. Other causes are advanced to explain inflammatory changes in the pancreas, notably trauma, action of digestive ferments in the pancreas and toxic changes following systemic disease.

If the causes of acute pancreatitis are difficult to ascertain, the diagnostic criteria are even more difficult to determine. A careful perusal of the literature will emphasize that the diagnosis of an inflammatory lesion of the pancreas is made more often at operation or necropsy than pre-operative. De Takats and MacKenzie[11] report 6 cases of acute pancreatitis, none of which was diagnosed prior to operation. In McWhorter's[12] series the diagnostic accuracy was 12%. Most commonly the diagnosis of perforated peptic ulcer or acute cholecystitis is made. Most of the patients found to have acute pancreatitis have had previous histories of abdominal pain and attacks described under the general term of indigestion, which may be interpreted as mild

attacks of pancreatitis or as evidence of conditions so frequently associated with acute pancreatic lesions. The pain associated with acute pancreatitis is, as a rule, severe enough to be prostrating, sudden in onset and, as a rule, persistent despite the administration of morphin. The most common position of the pain is in the epigastrium, though it has been reported as localized in every portion of the abdomen and at times widespread. Pain in the back likewise has been reported, as well as in either shoulder blade. Generalized rigidity is common but, as a rule, it is not the boardlike rigidity of a perforated ulcer. Tenderness, like the pain and rigidity, varies as to intensity and position. Vomiting is practically always present and is difficult to control. Early in the attack the temperature may be normal or subnormal, but it usually rises later. The white blood count is increased from 15,000 to 30,000. The blood sugar may be elevated and sugar may appear in the urine, but this is not common. The determination of amylase in the urine[13] and in the serum[14] is said to be diagnostic. These tests are seldom carried out and, due to difficulties of standardization, have not become popular. There appears to be a sound basis for the application of these tests in suspected cases since damage to the pancreas has been shown to cause a marked rise in serum and urinary diastase (personal observations). If the amylase determinations are to be worth much they must be carried out early in the course of the disease as after a rather short period, 1 to 3 days, normal values will be found. The Cammidge and Loewi tests, described as diagnostic tests for pancreatitis, are more difficult to explain on a rational basis.

Aspiration of the abdominal cavity has been suggested as a diagnostic measure, the finding of "beef broth" fluid being stated by Forbes[15] to be diagnostic. This procedure is not without hazard and the abdominal fluids found at operation have not been uniform in consistency or color.

The cause for the small number of cases diagnosed correctly before operation is not far to seek when one considers the variations in the clinical picture. The symptoms are likely to lead to a diagnosis of one of many acute abdominal inflammatory processes and the diagnosis is more likely to be made if the signs and symptoms of the condition most suspected are not clearcut.

In regard to treatment, most surgeons operate and drain the pancreas as early as possible. This feeling is not held universally, since Eliason and North[16] and Mikkelson[13] advise palliation. The mortality of the cases operated on is quite high—approximately 60%. Mikkelson reports a mortality of 7.5% in a series of 39 cases. It is difficult to determine the mortality of cases not operated on due to the difficulties of diagnosis, so that many may be diagnosed acute pancreatitis which are not definitely proven. The major difficulty in conservative treatment lies in the exclusion of perforation of a hollow viscus, since it might prove fatal to delay operation in these cases. The operation, as a rule, consists of drainage of the pancreas or an abscess if present. Drainage of the gall bladder or common duct is also advocated.

Acute pancreatic inflammatory lesions, whether they be of infectious nature or due to vascular changes in the pancreas, present symptoms of a severe nature which direct immediate attention to them and sug-

gest the serious nature of the illness. That the pancreas may undergo mild inflammatory changes with repeated recurrences is a possibility that has long been evident in medical and surgical thought. Many of the cases of so-called chronic pancreatitis have never been proven to have true inflammatory lesions of the pancreas. It is rather hard to determine the type of chronic inflammatory lesion which could cause the smoldering type of symptoms associated with this entity. Let it be said at the outset that those who speak of chronic pancreatitis do not have in mind any of the chronic granulomatous lesions, but think generally in terms similar to those associated with chronic appendicitis, a condition which many feel does not exist. The presence of fibrosis alone cannot be taken as evidence of chronic inflammation, but rather evidence of a previous acute inflammation or of vascular changes. The diagnosis of chronic pancreatitis is usually made at operation by feeling the head of the pancreas. If it feels larger and firmer than is usually considered "normal," in the presence or absence of gall bladder disease or a dilated common duct, this diagnosis is apt to be made. This basis of diagnosis is generally considered as the most convincing but the diagnosis depends on the experience of the surgeon and his ability to ascertain by the sense of touch actual changes in the head of the pancreas.

Gruber,[17] in a discussion of chronic pancreatitis, (Henke and Lubarsch[18]), states that the entire pancreas may be as hard as cartilage and yet show no evidence of acute or chronic inflammation. He quotes Heiburg as stating that it is impossible to determine the presence of chronic inflammation in the pancreas without examination microscopically. He further states that in reply to a questionnaire directed to surgeons by Guleke, it was found that some surgeons had seen but 10 to 20 cases in a 14-year period, one reported as many as 400 cases, and yet another stated that he had observed "numberless" cases.

De Tarnowsky and Sarma[19] state that the symptoms are in general those of biliary tract stasis. It is evident that the enlargement of the head of the pancreas may be considered as an associated phenomenon with lesions in contiguous or nearby structures. This viewpoint does not exclude the occurrence of a similar train of symptoms resulting from partial obstruction to the outflow of pancreatic juice or changes brought about in the parenchyma of the gland due to arteriosclerotic changes or prolonged general diseases. The question of so-called chronic pancreatitis is one which requires critical work and thought to determine the anatomic and physiologic basis for such an entity. The term pancreatitis refers to a pathologic process, the adjective "chronic" refers to the nature of the clinic course. It is necessary in order to clarify our thoughts on this subject to separate the connotations of this term and to separate as nearly as possible those cases which are primarily pancreatic in origin from those in which the pancreas is either secondarily involved or actually not involved at all.

Pancreatic lithiasis, cysts and traumatic rupture of the pancreas are fortunately uncommon. The diagnosis of pancreatic duct stone is, as a rule, made from Roentgen findings. The stones having a definite calcium content are radiopaque but may be wrongly interpreted as

calcified lymph glands. Ackman and Ross[20] review 54 cases and stress the varied symptomatology associated with pancreatic lithiasis.

With regard to rupture of the pancreas, Venable[21] reports 4 cases and presents observations gleaned from his own experience and a review of the literature. In general the problem is similar to that of rupture of other intraäbdominal solid viscera and early surgical intervention is required. The early symptoms are likely to be more severe than is the case with rupture of other intraäbdominal viscera.

The clinical features of inflammation of the pancreas offer many difficulties. The signs and symptoms, and even the classification of the pathologic processes, afford difficulties which defy any clearcut description. The symptoms which are associated with tumors of the islet tissue, however, are more readily understood and lend themselves more clearly to definition. These are in the main similar to those symptoms so commonly known by all who have had experience with insulin therapy. The conditions resulting from insulin overdosage have been common knowledge since the discovery of insulin by Banting and Best[22] in 1922, and the description of Banting and his associates[23] of the symptoms of "insulin shock." The concept that if the islands of Langerhans might be deficient in the production of insulin, so also an excess of this material might be elaborated by them, was presented by Seale Harris[24] a little over a year after the discovery of the active principle of the islands of Langerhans in a paper entitled "Hyperinsulinism and Disinsulinism."

Since Harris' paper numerous reports have appeared dealing with this subject. In recent months a most thorough review of the surgical aspects of hypersecretion has been presented by Whipple and Frantz.[2] Not only do these authors review the literature in a thorough and interesting manner, but also present a series of 6 cases with excellent results from operative intervention.

It is interesting that all of the patients reported by Whipple and Frantz were seen in the Neurological Institute where they were sent because of nervous disturbances. These consisted of spells of unconsciousness, somnolence, mental confusion, sweating, dizziness, giddiness, disorientation, diplopia and amnesia. Personality changes occurred in several. In all, there were found low blood sugar values even as low as 25 mg. per 100 cc. The symptoms were relieved after the administration of glucose, with the resultant increase in blood sugar. In all the cases a pre-operative diagnosis of islet cell tumor was made, and at operation one or more of these tumors were found. In one case after the removal of one tumor the patient's blood sugar remained low and it was necessary to reoperate and remove another tumor which had been overlooked at the first operation. The authors call attention to the fact that it is necessary to examine the pancreas carefully for other nodules, even though one is found. All these patients were relieved of their symptoms and their blood sugar values returned to and remained at normal levels.

It must be pointed out that the finding of a low blood sugar in association with neurologic symptoms or mental aberrations is not sufficient for the diagnosis of hyperinsulinism resulting from islet cell tumor. Wauchope[25] classifies the conditions which produce hypoglycemia, in addition to excess of insulin as follows: 1, lack of opposing secretions

due to disease of the adrenals, pituitary, or thyroid gland; 2, lack of glycogen due to destruction of reservoirs, as in disease of the liver, wasting of muscles; abnormal excretion of sugar, as in renal diabetes or lactation; active depletion of stores, as in muscular exercise, and failure to replenish stores, as in starvation; 3, interference with the regulating center, as in disease affecting the pons or overaction of the vagus. It is, therefore, necessary to rule out causes other than excess of insulin before an operation for the removal of an adenoma of the pancreas is considered. Common conditions suspected in the cases of adenomata of the pancreas reported in the literature are epilepsy, drunkenness, brain tumors and encephalitis. One of the patients reported from the Barnes Hospital, where the experience with hyperinsulinism has been quite extensive, was thought to have epilepsy,[26] another was thought to have a brain tumor.[27] One patient, operated on in our clinic and in whom adenoma was found, was sent to the neurosurgical service with the suggested diagnosis of a brain tumor (to be reported by Ravdin and Lukens). One of Whipple's patients, as well as one reported by McClenahan and Norris,[28] was thought to have had encephalitis.

Seale Harris[29] points out that the incidence of hyperinsulinism is greater than it is ordinarily thought to be. The severe cases presenting striking pictures and relieved by surgery certainly do not constitute the entire number of cases. Harris believes hypoinsulinism to be almost as common as diabetes. Of 3000 cases, he reports 500 cases of diabetes and 250 of hypoglycemia. Many patients have only mild symptoms and can be controlled entirely by diet. In a later paper Harris[30] points out that often the symptoms simulate various forms of gastro-intestinal disease.

The best results following surgical removal have been obtained in those patients in which adenomata have been found. Cases in which carcinomata have been found[31, 32] and in which metastases also were found were not helped by operation. The exact nature of the tumors removed from the pancreas, in the cases which obtained relief from their symptoms, is in most instances difficult to determine. Some tumors were well encapsulated but many were not. The structure of the masses removed from the 5 cases studied at Barnes Hospital has been reported by O'Leary and Womack.[33] But one of these tumors had malignant characteristics.

Following the removal of a tumor from the pancreas of a case to be reported by Ravdin and Lukens, an attempt was made to transplant some of the tissue into a diabetic with the hope that the cells would proliferate and reduce the insulin requirements of the recipient. The graft, however, was not successful. Tissue cultures were also made of the tissue in the hope that after cultivation a transplant could be effected, but these were likewise unsuccessful. A similar thought was evident in association with the cases of Whipple and Frantz,[2] as Murray and Bradley[34] reported attempts similar to ours. Direct transplantation of tissue from one patient to another has proven to be futile in the majority of instances. According to the work of Stone, Owings and Gey[35] on cultivation and transplantation of parathyroid tissue, the best chance of a successful transplant seems to lie in the transplantation of cultured tissue. Whether islet cells transplanted in this manner

will prove successful in alleviating the need for insulin therapy is problematical but it deserves further study.

Isolated tumors of islet tissue have not been found at operation in all reported cases of hyperinsulinism. Whipple and Frantz[2] emphasized the difficulties of finding adenomata, especially where the tumor lies within the substance of the pancreas. It is possible that in some instances tumors are overlooked even after a most careful search. In many of these cases a portion of the pancreas has been removed, but the results have not been gratifying. Except in a few cases the symptoms have returned following operation. Holman and Railsback[36] suggest that in order to be effective, four-fifths of the entire pancreas should be removed.

The removal of a portion of the pancreas or the excision of an adenoma is a surgical procedure of major proportions and the operation should be considered with some circumspection. The mortality following removal of adenomata of the pancreas, however, has been negligible. Whipple and Frantz[2] attribute this to the skill of the surgeons who have attempted the operation, and not to the simplicity of the operation itself. The low mortality will probably not be maintained as the popularity of the procedure increases. The importance of the experience and skill of the surgeon is emphasized by elective procedures carried out on the pancreas.

Within recent years successful attempts have been made to remove carcinoma of the ampulla of Vater by Parsons and Mullins[37] and Walters.[38] Surely this is not a procedure for the novice. Carcinoma of the ampulla of Vater produces suffering and mortality due primarily to obstruction. The growth is, as a rule, slow and metastases are late. Selected cases in the hands of a competent surgeon are offered relief from this all too common disorder by resection of the growth and contiguous structures. In the past these cases have been relieved of obstruction by cholecystogastrostomy or cholecystoduodenostomy, a purely palliative procedure. Permanent relief to patients suffering from this disturbance which heretofore has been considered hopeless seems now to be within the scope of surgical therapy if seen early.

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OPHTHALMOLOGY

UNDER THE CHARGE OF
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OCULAR LESIONS IN DIABETES MELLITUS.

THE four most commonly considered ocular complications of diabetes mellitus are: 1, transient changes in refraction; 2, cataract; 3, retinitis, and 4, toxic amblyopia. The transient changes in refraction seem to have about the same frequency under insulin as under purely dietary therapy, but are not of serious import. It seems necessary to distinguish between true diabetic cataracts and senile or presenile cataracts occurring in the diabetic. The incidence of true diabetic cataract seems to have decreased since the use of insulin. Cases of toxic amblyopia are also seen less frequently in the group of diabetics now under careful management. Lipemia retinalis is rarely seen now. However, the incidence of retinitis in diabetics has apparently increased in recent years. Even though this apparent increased incidence is attributed, as it probably should be, to the increased duration of the life of diabetics under insulin therapy, the problem of diabetic retinitis is becoming more vital to all patients with diabetes because of the serious loss of vision in many cases. The factor in the disease which is directly responsible for the retinitis has not as yet been determined. It has not been con-

clusively demonstrated that the present methods of treatment prevent the onset or control the progress of diabetic retinitis. Folk and Soskin[3] believe that proper control of the diabetes along present lines is efficacious, but Gray[5] states, on the other hand, that control of the diabetes is without effect on the retinal lesions. Because of this uncertain status of the retinal complications, several extensive studies of the eyes in diabetics have been carried out in recent years. While no definite conclusions have been reached in any of these studies, it would seem worth while to review the data obtained, particularly in the investigation carried out by Waite and Beetham.[8]

A number of different types of retinitis have been described in association with diabetes mellitus. It seems quite probable that all these types, from the central punctate retinitis of Hirschberg to the retinitis with marked disease of the veins and retinitis proliferans, represent progressive stages of the same initial lesion, complicated in some instances by changes associated with hypertension and arteriosclerosis and in the cases of hemorrhages into the vitreous and retinitis proliferans, possibly with the added factor of tuberculosis or of focal infection as pointed out by Gray. It is true, as pointed out by Folk and Soskin, that the small, punctate, deep hemorrhages in the retina and central punctate retinitis are usually associated with minimal, if any, visible changes in the retinal arterioles, and often occur in cases of diabetes without demonstrable vascular complications. Arteriolosclerosis is constantly assuming more importance in diabetes. It is probable that the occurrence of these retinal lesions is in itself evidence of vascular disease in the capillaries and probably on the venous side of the capillary loop. Also it can readily be demonstrated that other vascular complications are much more frequent in diabetic patients with retinitis than in those without retinitis. Thus, in the series reported by Wagener, Dry and Wilder,[7] the blood pressure was found to be elevated in 66% of diabetics with retinitis and in 46% of those without retinitis. A diagnosis of disease of the arteries or kidneys was made in 84% of the patients with retinitis and in 53% of those without. Diabetic neuritis, usually thought to be of vascular origin, was present in 25% of the group with retinitis, and in 8% of those without. Again, Gray found the general incidence of diabetic retinitis to be 13%, but retinitis was present in 40% of his patients with gangrene of the extremities.

Gray made a study of the intraocular arterial pressure by the dynamometer method of Baillart in 62 cases of diabetic retinitis. His findings were not uniform or conclusive. The pressure was normal in 8 cases, low in 20, and high in 34.

Waite and Beetham[8] have attempted to correlate various individual features of the retinitis with certain factors in the general disease. Thus the incidence of deep retinal hemorrhages, the feature most common to all cases of retinitis in diabetes, was found to increase definitely with increase in the age of the patients and with increase in the degree of retinal arteriosclerosis. That the occurrence of hemorrhages was not due directly to arterial hypertension was shown by the fact that considerably more than half of them occurred in patients with blood pressures within the normal and high normal range. There was no obvious causative relationship between renal disease and hemorrhages in the retina, since only 6% of the patients with hemorrhages showed blood

non-protein nitrogen values of over 44 mg. %. Yet only 18% of the patients with non-protein nitrogen values in the blood of less than 35 mg. % showed hemorrhages in the retina, while hemorrhages were present in 30% of the diabetics with non-protein nitrogen above 50 mg. %. All these facts indicate the higher incidence of hemorrhages in diabetes with complicating vascular and renal disease.

The relationship between hemorrhages in the retina and duration of the diabetes is quite definite. Thus hemorrhages were found in 6% of the cases of 1 year's duration, and in 20% of the cases of 5 to 10 years' duration, while the average age of the patients was approximately the same in each group. Hemorrhages were present in 43% of the cases of 10 to 15 years' duration and in 59% of the cases of over 15 years' duration. Thus there is a definite increase in the incidence of hemorrhages with increased duration of the diabetes disproportionate to the increased age of the patients.

That the use of insulin is apparently not a factor in causing the hemorrhages is shown by the fact that only 1.7% of the patients with hemorrhages in the retina were taking 50 units or more of insulin daily, while 4.5% of the total group of diabetics were using this amount.

No obvious relationship could be demonstrated between hemorrhages and blood calcium or blood sugar levels. Blood calcium was estimated in 9 patients with hemorrhages. It was slightly below normal in one. Only 7% of the patients with hemorrhages showed fasting blood sugars of over 300 mg. %.

Waxy exudates occurred in about 10% of the diabetics examined. Their incidence increased with the age of the patients, a sharp increase in incidence being noted in patients over 50 years of age. The exudates also increased in frequency with greater duration of the diabetes, being present in approximately 10% of the cases of 5 to 10 years' duration, in 30% of the cases of 10 to 15 years' duration, and in 40% of the cases of more than 15 years' duration. They may arise through hyalinization of deep retinal hemorrhages.

Hemorrhages in the nerve fiber layer of the retina apparently have no characteristic incidence in diabetics. They were found in 5% of the patients, and 83% of them were found in association with the characteristic deep hemorrhages. It is interesting to note that in diabetes their incidence increased with increase in the age of the patients, while, in the group of non-diabetics selected for comparison, their incidence decreased with increase in the age of the patients. Cotton-wool patches likewise showed a rising percentage by decades of life in the diabetics, and a falling percentage in the non-diabetics. They were found in 4% of the diabetics examined. Their occurrence was not related apparently to increased non-protein nitrogen in the blood. Apparently, their relationship to arterial hypertension and the relationship between retinitis and fat metabolism was not studied.

It would seem that the only definite conclusion to be drawn from these studies of Waite and Beetham is that the duration of the diabetes is more definitely a factor in the causation of retinitis than is its severity. It still seems impossible to say what feature of the diabetic disease accounts for the greater frequency of deep retinal hemorrhages in diabetics than in non-diabetics of similar age groups. Waite and Beetham think that "all evidence points to the capillaries as the source

of these hemorrhages We should seek more information about the physiology and pathology of the retinal capillaries, about their normal and abnormal hydrodynamics, about glycogen deposits which are known to affect other ocular tissues, about the normal and abnormal permeability of capillary walls, about thromboses which may form within them, and about toxins which may affect them adversely."

Waite and Beetham found in 31 of their 2002 diabetics (1.5%) preretinal hemorrhages or proliferation of vessels and connective tissue in the retina and vitreous. All of these patients were over 40 years of age, 21 of them were between 40 and 60. In 83% of this group there was marked disease of the retinal arteries and veins, which latter might be the source of the hemorrhages. The diabetes was severe in only a small percentage of the cases. The use of insulin was not connected with their development, and iodids were thought to be harmful. The prognosis is poor. Careful diabetic management does not check their progress.

The rôle of diabetes in the etiology of retrobular neuritis or toxic amblyopia is open to considerable question. Several years ago, Francis endeavored to show that ketosis was responsible. This has not been proved. The lesion may be arteriosclerotic in character. Waite and Beetham found 7 cases among their 2002 diabetics. All the patients were more than 52 years of age and showed considerable retinal arteriosclerosis. They believe, however, that the amblyopia is really due to tobacco, to which the diabetics are particularly susceptible.

The transitory changes in refraction to which the diabetic is subject at the onset of the disease and upon the initiation of treatment are of considerable interest. They are of importance, inasmuch as the occurrence of a rapid change in refraction without visible evidence of ocular disease should suggest the presence of diabetes and inasmuch as it is never wise to prescribe glasses during the early phase of diabetic management when there is likelihood of rapid shifts in blood sugar levels. Himsworth[6] states that transient myopia occurred as an initial symptom in 49% of 47 cases under 45 years of age, and in 23% of 53 cases over 45 years, an average of 34%. In studying the refraction of patients who were starting a course of diabetic management, Granström[4] found increased hyperopia in 57 of 80 previously untreated cases, and in only 7 of 38 who had had previous periods of diabetic treatment. The explanation of these changes probably lies, as suggested by Duke-Elder,[2] in the change in the index of refraction of the lens, due to the upset in osmotic balance between the chlorid content of the lens and that of the aqueous which occurs along with rapid shifts of the sugar and chlorid content of the blood. Waite and Beetham noted transient changes of refraction in only 6% of their patients, but this percentage was on the basis of history alone, since all their cases were not refracted under cycloplegia. They were able to demonstrate a weakness of accommodation in 40% of the 58 patients with transient hyperopia who were under 50 years of age, while in the entire group of diabetics, 21% showed demonstrable weakness of accommodation. Both these conditions tended to disappear under proper diabetic regimen.

Waite and Beetham made extensive slit-lamp studies of the cornea, iris and lens. The incidence of arcus senilis was the same in diabetics as in non-diabetics. Wrinkles in Descemet's membrane of the cornea

were found to increase with the age of the patient but were present in 26% of the diabetics as against 10% of the non-diabetics. In diabetics the wrinkles were found to appear earlier and to be more numerous in the individual eye. Among the diabetics, wrinkles were found in 60% of the gangrene cases, in 51% of the deep retinal hemorrhage cases, and in 43% of the diabetic neuritis cases.

Depigmentation of the iris was found in 6% of diabetics as compared with 2% of non-diabetics. This is probably due to a more facile release of pigment from the uveal tract of the diabetic as can be demonstrated by massaging the eye during slit-lamp examination or on opening the anterior chamber surgically. Correspondingly, pigment deposits were found on the posterior surface of the cornea in 11% of diabetics and in 5% of non-diabetics. A possible cause of this may be damage to the iris pigment epithelium through selective glycogen storage. Histologically, Waite and Beetham have been able to demonstrate "abnormal glycogen deposits in the retina and optic nerve, in the epithelium of the lens capsule, and especially in the pigment epithelium of iris and ciliary body, which may show an increase of many times its normal thickness due to glycogen alone."

It is of interest that among their 2002 diabetics, Waite and Beetham found 10 patients with Argyll-Robertson pupils, in 5 of whom no evidence for the diagnosis of syphilis could be elicited.

The results of Waite and Beetham's slit-lamp examinations of the lenses of diabetics and non-diabetics are of considerable interest in that, in patients over 20 years of age, opacities were found by the slit-lamp in 50% of diabetics and in 57% of non-diabetics. This would seem to refute the usual assumption that cataract occurs more frequently in diabetics. Among 297 juvenile diabetics, 11 patients with "flocculi" cataracts were found (4%). These are the supposedly typical diabetic cataracts but they seem to be indistinguishable from the cataracts of parathyroid tetany, scleroderma or myotonic dystrophy. In half of these patients, the diabetes was poorly controlled at the time of observation, but in the other half the opacities appeared and progressed in spite of most satisfactory control of the diabetes.

Carey and Hunt[1] report a study on the chemical nature of cataract in the diabetic in the course of which they analyzed for cholesterol, total calcium and total non-lipoid phosphorous 10 normal lenses, 13 cataractous lenses of diabetic patients (not the juvenile flocculi cataracts), and 30 cataractous lenses of non-diabetic individuals. They found that the normal lens contains approximately 400 mg. % cholesterol, 9.5 mg. % calcium, and 16.5 mg. % phosphorus. The cataractous lens contains 522 mg. % cholesterol (20% more than the normal lens), and 31.6 mg. % calcium (three times normal lens or blood). The cataractous lens of the non-diabetic contains 19.7 mg. % of phosphorus (slightly more than normal), but the cataractous lens of the diabetic contains 6.2 mg. % phosphorus (less than half the normal). They state: "The cataract forming in the eye of the diabetic appears chemically to be the classical senile cataract in all respects save one. The phosphorus metabolism is markedly different. What importance this has one does not know at present."

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 16, 1935

A Bloodless Method for Continuous Recording of the Peripheral Circulation and its Application in Physiology and Pharmacology.—HANS MOLITOR and MICHAEL KNIAZUK (Merck Institute of Therapeutic Research, Rahway, New Jersey). A bloodless method for studying of the peripheral vascular circulation is described, based on on the principle of simultaneous recording of surface temperature and light transmission through the skin. A rabbit's ear is placed between a steady source of light and a photocell. Vasodilation decreases the amount of light transmitted through the skin and consequently lowers the current output from the photocell; the opposite effect takes place during vasoconstriction. In order to differentiate between active hyperemia and passive congestion, the surface temperature of the area under observation is measured thermoelectrically. During active hyperemia the skin temperature is increased, while during passive congestion it remains either unchanged or is lowered. The current fluctuations produced by the photocell and the thermocouple are continuously recorded on a paper kymograph. The method is not only useful for the analysis of vasoconstricting or dilating drugs but can also be applied to the investigation of local and general anesthetics and sedatives, based on the observation that the ear vessels of the rabbit respond with vasoconstriction to almost any type of mechanical or sensory stimulus, whether applied to the ear or other parts of the body.

The Effect of Combination with Diazo Compounds on the Immunological Reactivity of Antibodies.—HARRY EAGLE, DOROTHEA E. SMITH and PERCY VICKERS (Laboratory of Bacteriology, University of Pennsylvania). Sufficient coupling with diazo compounds eventually destroyed the reactivity of all the antisera here studied. This was due to the progressive and simultaneous decrease in the reactivity of all the anti-

body molecules, rather than the inactivation of an increasing proportion of molecules. The rate of inactivation varied considerably among the several antisera. By stopping the reaction at intervals, it was possible to prepare partially inactivated antisera of peculiarly modified reactivity.

Thus, the flocculating activity of diphtheria antitoxin with toxin was completely destroyed long before there was any demonstrable impairment of its protective titer *in vivo*. The first change induced in antipneumococcus horse sera was the complete loss of reactivity with the capsular carbohydrate at a time when the agglutinating, animal-protecting, and complement-fixing activities of the sera were only slightly affected. On further coupling, the sera no longer caused visible agglutination; but aggregation of the serum-treated bacteria could be induced by centrifugation. Still further coupling destroyed all antibody activity.

Rabbit antisera to egg albumin and horse serum no longer precipitated the homologous antigen after treatment with diazo compounds, due to their failure to combine with the antigen. The hemolytic, complement-fixing and lipoid-flocculating activities of coupled rabbit antisera to sheep red blood cells fell off in parallel; the hemagglutinin seemed somewhat more resistant. The reagin of syphilitic serum was destroyed almost instantaneously by comparatively small amounts of diazo compounds. Finally, in the case of antityphoid agglutinin, the isoelectric point of the coupled antibody, measured on the surface of specifically sensitized bacteria, was found to shift from an original value of pH 4.7 to one of less than pH 2.7 as progressively more sulfanilic acid radicals added on to the antibody molecule.

The groups in protein which participate in its reaction with diazo compounds probably include aliphatic amines, the imidazole ring of histidine, the indole group of tryptophane, the NH of proline and hydroxyproline, and the phenolic group of tyrosine. The properties of the coupled antibody suggest the extent to which these groups participate in the combination of antibody with antigen, and the extent also to which they may be responsible for the characteristic properties of the antigen-antibody compounds.

The Behavior of Polymorphonuclear Leukocytes Outside the Bloodvessels.—E. R. CLARK and E. L. CLARK (Laboratory of Anatomy, University of Pennsylvania). Polymorphonuclear leukocytes were studied microscopically in the living animal, in the transparent tails of Amphibia and in transparent chambers installed in rabbits' ears, where they were observed in circulating vessels, in the act of migrating through vessel walls, in the outside tissue and in the interior of blocked lymphatics.

The process of emigration of individual leukocytes from bloodvessels was the same in Amphibia and mammal. Polymorphs which emigrated following endothelial changes, in the absence of any localized focus of attraction in the tissue, moved around rapidly at random for the first 24 hours, after which they became more sluggish and finally, after 4 to 6 days, rounded up and remained motionless. In the rabbit, phagocytosis of such rounded cells by macrophages was observed.

In microinflammations produced by injecting dilute croton oil into tadpoles' tails, polymorphs observed continuously in the living were seen to migrate toward the croton oil, to become stationary at a short

distance from it, to lose their granulation and send out fine processes, while still retaining their polymorphic nuclei. In specimens fixed and stained at this stage, 95% of the leukocytes in the inflammation area, exclusive of macrophages, were polymorphonuclear. Following extrusion of the oil, the polymorphs, after temporarily resuming their amœboid form, again became stationary in a rounded form. In specimens fixed in this later stage (24 to 48 hours), counts of leukocytes, exclusive of macrophages, showed 75% to be mononuclears. Disintegration of leukocytes was limited to a few cells. Observation of all the connective-tissue cells and endothelial nuclei of the entire area of inflamation over periods of 40 hours excluded the possibility of the transformation of such cells into any form of leukocyte and continuous observation of all the surrounding bloodvessels failed to show any secondary emigration from the blood stream. Furthermore, in a number of experiments individual polymorphs were watched continuously and the rounding up of these cells and the subsequent coalescence of their nuclear material into a mononuclear form was followed with camera lucida records.

In the rabbit, some polymorphs were observed to enter blocked lymphatics following emigration from a nearby vein, where they frequently remained corralled in the bulbous end of a lymphatic for weeks with no subsequent emigration of fresh leukocytes from the blood stream. When the same group of imprisoned cells was followed from day to day, the leukocytes which were at first easily identifiable as polymorphs, gradually assumed a rounded form with round nuclei, lost their granulations, and became smaller. When such specimens were fixed and stained the cellular contents of such a blocked lymphatic had the picture of a "round-cell infiltration."

The changes observed in polymorphs, which remained for some time outside the blood stream, into round mononuclear cells was evidently a simulation of, rather than a true transformation into, monocytes or lymphocytes, since the behavior of such changed leukocytes and the fact that they were frequently phagocytized by macrophages showed them to be partially degenerated cells. However, the strong resemblance of collections of leukocytes, known from their past history in the living animal to have been typical polymorphs which emigrated from the blood streams, to the mononuclear exudates and round cell infiltrations of pathologic material, suggests the possibility that the latter may be, in part at least, composed of changed polymorphs.

It is obvious that the conditions found outside the blood capillary, whether in the intercellular substance or in the interior of lymphatic vessels, furnish an environment which is unhealthy for the polymorphs. In their behavior here they contrast markedly with true monocytes, which thrive in the tissue spaces. We have seen them to continue, as macrophages, to manifest sporadic amœboid activity and capacity for phagocytosis for months.

Evaluation of Mercurial Antiseptics in the Presence of Serum.—DOROTHEA E. SMITH, E. J. CZARNETZKY and STUART MUDD (Laboratory of Bacteriology, University of Pennsylvania). Several mercurial antiseptics have been compared for their germicidal action in saline and in 80% serum. An accurate method of plating has been used, and the

time and concentration required for 50% killing of a culture of smooth *B. typhosus* has been taken as a basis of comparison.

Metaphen, merthiolate, mercurochrome and bichlorid of mercury all combine with serum proteins. When maximum combination is secured the resulting compounds possess no antiseptic action. The mercury content found by analysis of the equilibrium germicide-protein compound is the same, within the limits of experimental error, for all four germicides. Equilibrium has been approached in both directions. In one case an excess of mercurial was used, and in the other an excess of serum proteins. In the latter case, the rate of combination was determined by adding the calculated amount of mercurial and noting the time when the mixture no longer possessed antiseptic action. The ratio of the rate with which the mercury of the mercurials combines with bacteria and with serum proteins is more favorable in the case of some of the mercurials than with the others. These compounds kill bacteria, then, only in proportion to their mercury content. The decrease in germicidal activity when used in serum is equal to the amount of mercury chemically combined with serum. When used in saline, the killing power of the antiseptics is directly proportional to their concentration, but when used in serum, the killing power is proportional only to the concentration of antiseptics not combined with the serum proteins. It has been found that approximately 0.4 gm. as mercury of any of these mercurials can be bound by one liter of normal horse serum.

It follows that the effect of serum is such that neither metaphen, merthiolate, mercurochrome, nor bichlorid of mercury may be used as intravenous antiseptics.

ERRATUM.

The footnote referring to Dr. Rawls' article on agranulocytosis (p. 131, January issue of this JOURNAL) should read: "In a more recent communication, now in press, Rawls stresses the infrequency of agranulocytosis in a large series of amidopyrin cases."

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ORIGINAL ARTICLES.

PNEUMOCOCCUS TYPE III PNEUMONIA.

AN ANALYSIS OF 500 CASES.

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PNEUMOCOCCUS Type III pneumonia has always aroused the interest of medical men, partly because of the peculiar morphologic, biologic and chemical properties of pneumococcus Type III, but chiefly because of the generally recognized severity of this type of pneumonia. There, however, is comparatively little in the medical literature concerning Type III pneumonia as a clinical entity. Among the statistical studies which deal with the incidence and death rate for the various types of pneumonia should be mentioned the studies of Dochez and Gillespie,[1] Dochez and Avery,[2] Cole,[3] and Bullowa.[4] In 1927, Cecil, Baldwin and Larsen,[5] in a statistical study on 2000 typed cases of lobar pneumonia, pointed out certain clinical features of the various types. In this article it was first brought out that Type III pneumonia was particularly common in elderly people and that the incidence of this type was higher in

women than in men. It was also shown that Type III pneumonia was especially prevalent in patients with some chronic systemic disease. All writers on this subject are agreed that Type III pneumonia has in general a much lower incidence than Type I or Type II infections, and that the death rate is high (in most reports from 40 to 50%). Blake,[6] in a recent report on 122 cases of Type III pneumonia studied in the wards of the New Haven Hospital, corroborates the findings of Cecil, Baldwin and Larsen, and stresses the fact that, though Type III pneumonia has a high death rate, it is no more fatal than other types when it occurs in young and healthy people.

In Blake and Cecil's[7] experimental Type III pneumonia in monkeys (intratracheal injection of small doses of pneumococcus Type III culture), the disease ran a characteristic mild course. More recently, Francis and Terrell[8] have produced experimental Type III pneumonia in monkeys by insufflation of pneumococcus Type III culture deep into the trachea and bronchus by means of a soft rubber catheter. They found that the severity of the disease was roughly proportional to the amount of culture injected and that the death rate for experimental Type III pneumonia in monkeys was directly proportional to the height of the septicemia accompanying the pneumonia.

Sugg[9] and his co-workers were the first to call attention to an "atypical" Type III pneumococcus. They found it to be closely related immunologically to typical strains, and pointed out how readily it could be confused with the latter in routine typing because of the high degree of cross-agglutination which may occur between the two types with some diagnostic serums. In the revised classification of pneumococci by Cooper,[10] the atypical pneumococcus Type III has been designated pneumococcus Type VIII.

Finland and Sutliff[11] have recently contributed an interesting comparative study of the clinical features of pneumonia as produced by pneumococcus Type III and Type VIII respectively. For example, they show that Type VIII pneumonia, like Type III, is much more common in females than in males, and that chronic disease was a common predisposing factor in both Type III and Type VIII infections.

The present study is based on material which has been collected during the past decade or more in the wards of Bellevue Hospital, and is really a continuation of previously published studies on the various types of pneumonia (Cecil and Plummer[12]). In addition to material from the adult medical wards, 9 cases of Type III pneumonia from the pediatric service at Bellevue Hospital are included.

Incidence. As already mentioned, pneumococcus Type III pneumonia has a much lower incidence than either Type I or Type II infections (Table 1). In 4310 pneumococcal pneumonias,

Type I infections were the most frequent (32.1% of the whole series); Type II ranked next with 23%, while Type III comprised only 11.1%.

TABLE 1.—INCIDENCE OF DOMINANT TYPES OF LOBAR PNEUMONIA IN BELLEVUE HOSPITAL, 1920–1931.*

Type of pneumococcus.	No. of cases.	Incidence, %.
Type I	1384	32.1
Type II	991	23.0
Type III	477	11.1
Misc. types	1458	33.8

* 1925–1926 cases are omitted from this series.

A comparison of the incidence of Type III pneumonia in Bellevue Hospital and in other institutions in New York and New Haven (Table 2), reveals that the incidence of Type III pneumonia is remarkably constant in three large New York hospitals. A higher incidence was found in the New Haven Hospital, and may be explained by differences in environment, type of patient admitted, etc. When the total of 765 Type III cases included in these reports is averaged, the incidence of Type III pneumonia is 11.8% of the entire pneumococcal series. Approximately 1 in every 8 cases of lobar pneumonia is a Type III infection.

TABLE 2.—COMPARATIVE INCIDENCE OF DOMINANT TYPES OF PNEUMONIA IN FOUR HOSPITALS.

Type of pneumococcus.	Bellevue Hospital. (Cecil.)		Rockefeller Hospital. (Cole.)		Harlem Hospital. (Bullowa.)		New Haven Hospital. (Blake.)	
	No. of cases.	Incidence, %.	No. of cases.	Incidence, %.	No. of cases.	Incidence, %.	No. of cases.	Incidence, %.
Type I	1384	32.1	403	36.3	112	31.0	194	32.0
Type II	991	23.0	249	22.4	69	19.0	79	13.0
Type III	477	11.1	123	11.1	43	12.0	122	20.0
Misc. types	1438	33.8	335	30.2	141	38.0	211	35.0

Incidence of Type III Pneumonia in Children. In 329 cases of pneumonia in children at Bellevue Hospital, Raia, Plummer and Shultz[13] found only 10 cases of Type III pneumonia. All 10 of these occurred in children under 3 years.

Incidence According to Age. Cecil, Baldwin and Larsen[5] were the first to point out that Type III pneumonia constituted 33.7% of all pneumococcal pneumonias in patients over 60 years, which was almost twice as high as the incidence of Type I or Type II pneumonia in this age group. If one considers *only* the Types I, II and III infections in the present series, 45.8% of all cases over 60 years were Type III infections, while if *all* types are included, pneumococcus Type III constituted 32.8% of the cases over 60 (Table 3). In contrast to these figures, in patients under 50, only 9.4% were suffering from Type III infections.

TABLE 3.—INCIDENCE OF TYPES IN RELATION TO AGE.

Type of pneumococcus.	Under 50 years.		Over 50 years.		Over 60 years.	
	Cases.	%.	Cases.	%.	Cases.	%.
Type I	1056	33.8	194	22.6	63	18.8
Type II	785	25.2	249	28.9	77	22.9
Type III	292	9.4	208	24.2	110	32.8
Misc. types	986	31.6	209	24.3	85	25.5

Blake found the preponderance of Type III infections even more marked in elderly patients. In his series, 70% of all patients over 60 years with Types I, II or III pneumonia were Type III infections.

Figure 1, based on our own cases in Bellevue Hospital, illustrates graphically the comparative age incidence of Types I, II and III pneumonia according to decades.

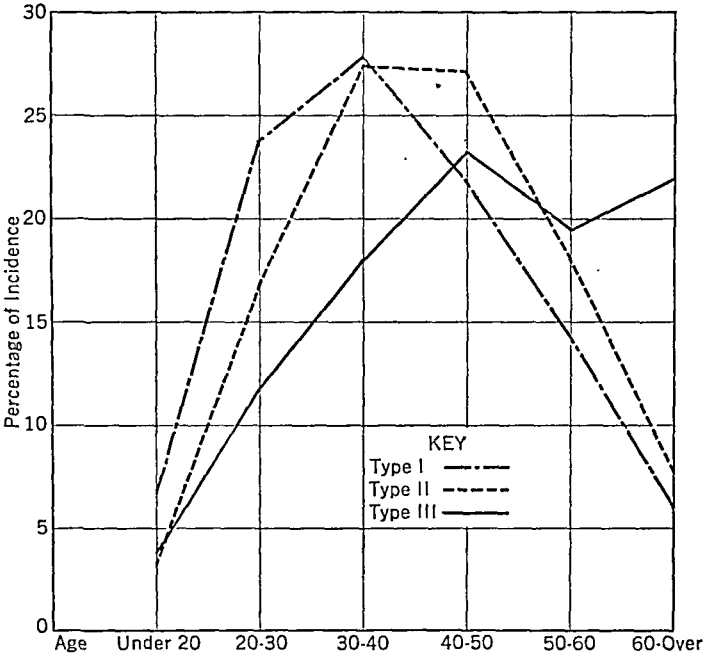


FIG. 1.—Incidence of pneumococcus Types I, II and III pneumonia in relation to age.

It will be noted that the incidence curves of Type I and II pneumonia run almost parallel, both reaching their highest points between 30 and 50, and falling off rapidly during the later decades of life. On the other hand, the incidence curve of Type III pneumonia ascends more gradually, reaching its highest point at the age of 50 and maintaining a high level during the remaining decades of life. Of the adult Type III pneumonias, 64.8% occurred in patients past 40. This figure compares favorably with that of Finland and Sutliff, who found 69% of their Type III infections in patients over 40.

Incidence of Type III Pneumonia According to Sex. In the

present study the number of Type III pneumonias in males exceeds that in females (392, or 78%, males, and 108, or 22%, females). In statistical studies all types of lobar pneumonia appear to occur more frequently in males than in females, but this apparent preponderance of males may be due, at least in part, to the fact that there are always more male than female patients in city hospitals. Females, however, are apparently more susceptible to Type III infections than males, for the *incidence per cent* is 18.2% for females, as compared with 11.6% for males (Table 4). This is in sharp

TABLE 4.—INCIDENCE OF TYPES IN RELATION TO SEX.

Type of pneumococcus.	Total males.		Total females.	
	Cases.	%.	Cases.	%.
Type I	1108	32.7	142	23.9
Type II	956	28.2	78	13.1
Type III	392	11.6	108	18.2
Misc. types	929	27.5	266	44.8

contrast to Type I and Type II infections, where the incidence per cent for the two latter types is considerably higher for males than for females.

Incidence of Type III Pneumonia in Relation to Age and Sex. In Table 5 the combined influence of age and sex on the incidence of Type III pneumonia is indicated.

TABLE 5.—INCIDENCE OF TYPES IN RELATION TO AGE AND SEX.

Type of pneumococcus.	Males under 50 years.		Females under 50 years.		Males over 50 years.		Females over 50 years.	
	Cases.	%.	Cases.	%.	Cases.	%.	Cases.	%.
Type I	930	35.0	126	26.7	178	25.0	16	13.0
Type II	720	27.2	65	13.7	236	33.1	13	10.6
Type III	231	8.8	66	13.6	138	19.4	45	36.6
Misc. types	769	29.0	217	46.0	160	22.5	49	39.8

In both groups, that is, in patients under 50 as well as in those over 50, Type III pneumonia is twice as common in women as in men, and it is four times as common in women over 50 (36.6%) as it is in men under 50 (8.8%). This table further shows that in females over 50, infections with Type III and the miscellaneous types cause 76.4% of all pneumonias, while in males under 50 they cause only 37.8% of the cases. These latter figures have considerable significance with respect to serum therapy; two-thirds of the pneumonias in men under 50 will be Type I or Type II infections and, therefore, amenable to serum treatment.

Incidence by Season. There appears to be very little difference so far as seasonal distribution is concerned between the incidence of the three dominant types of pneumonia. (Fig. 2.)

In all three types the incidence is highest in January, February and March. Then begins a rapid descent, striking the lowest point in early summer and continuing there through September.

In October the curves begin to rise again; 79% of all the Type III pneumonias were admitted to the hospital between December and May, inclusive.

Relation of Type III Pneumonia to Chronic Disease. Pneumococcus Type III pneumonia is two to three times as apt to occur in individuals who are already the victim of some chronic disease as are Types I and II pneumonias. This was first pointed out by Cecil, Baldwin and Larsen, and has recently been confirmed by Blake who found that 79 of 119 cases of Type III pneumonia were victims of some chronic systemic condition. Blake points out that this was not entirely the result of advancing years, as 19 of 32 patients with Type III pneumonia between 20 and 50 years suffered from chronic disease.

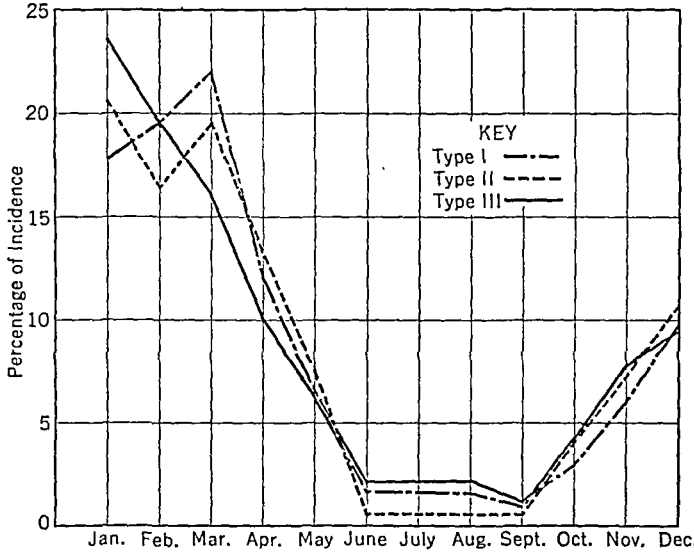


FIG. 2.—Incidence of pneumococcus Types I, II and III pneumonia in relation to season.

In the present study, 49.9% of the Type III patients were afflicted with some chronic malady, a considerably higher proportion than for either Type I or Type II infections (Table 10). Of these cases with chronic disease, 24 were under 30 years. Alcoholism and degenerative cardiovascular disease lead the list. The mortality in chronic alcoholic patients was very high—almost 50%. There was a death rate of 77% for patients with chronic cardiovascular disease.

Clinical Features. Clinically Type III pneumonia shows no special characteristic features which would differentiate it from the other types of pneumonia. The onset was described as sudden in 52% of the cases. The two most common initial symptoms were chill and pain in the chest. It was found that the right lung only

was involved in 226 cases, as compared to 168 with left-sided consolidation. In single lobe involvement the right lower lobe was most frequently affected.

Duration of Disease. Cecil, Baldwin and Larsen, in their study of 2000 typed pneumonias, found that pneumococcus Type III pneumonia ran, on an average, a somewhat longer course than either Type I or Type II infections. The average duration of the Type III series was 9.1 days, as compared with an average duration of 8.8 days for Type I pneumonia and 8.6 days for Type II pneumonia. Blake found that in Type III pneumonia affecting individuals past 50, that is, during the period of high susceptibility, the disease ran a longer course than it did in those under 50, and that in the elderly group recovery was nearly always by lysis rather than by crisis.

In the present study, termination, if by crisis, usually occurred before the eighth day; if by lysis, on or after the eighth day. Crisis occurred in 153 cases *under* 50 years (52.3%), as compared with only 32 cases *over* 50 years (15.3%). It was found that complications occurred in only 4.8% of patients who recovered by crisis, as compared with 19.7% of patients who recovered by lysis.

Bacteriemia. Blood cultures were taken on one or more occasions in 198 cases. Positive cultures were found in 55 (29.4%). This figure approximates closely the Harlem Hospital figures as reported by Rosenbluth[14] (25%) and those of Finland and Sutliff (34%). Blake, reported bacteriemia in only 8% of his Type III series.

Eight of our Type III patients with positive blood cultures recovered. Two of these showed positive plate cultures, while the others were positive in broth only. One patient, a male, aged 41, and an alcoholic, had 100 colonies of pneumococcus Type III per cc. of blood, and recovered. In the fatal cases, bacteriemia was present before the fifth day in 43 of the 47 cases. In 4 septic cases the blood cultures became negative before death. All of the septic patients who recovered were under 50 years of age. Invasion of the blood stream by the hemolytic streptococcus was observed in 3 patients with Type III pneumonia, and 1 of these recovered.

It is interesting to compare the incidence of bacteriemia in Type III pneumonia, with its incidence in Type I and Type II infections, as observed in the Bellevue Hospital studies (Table 6). In our experience the incidence of bacteriemia in Type III pneumonia is about the same as that for Type I cases. Both types show a considerably lower incidence of bacteriemia than Type II infections. The death rate for all bacteriemic cases is very high. It is noteworthy, however, that while the incidence of bacteriemia in Type I and Type II pneumonia coincides closely with the death rate for these types, respectively, in Type III infections the death rate is considerably higher than the incidence of bacteriemia. In other words, some patients with Type III pneumonia die without sepsis.

TABLE 6.—COMPARATIVE INCIDENCE OF BACTEREMIA IN THE DOMINANT TYPES OF PNEUMONIA.

Type of pneumococcus.	Cases cultured.	Bacteriemia, %.	Death rate, %.	
			Bacteremic cases.	Entire series.
Type I	64	29.7	66.7	28.2*
Type II	133	51.1	87.5	48.8*
Type III	187	29.4	85.4	42.2*

* None received serum.

Complications. The complications of Type III pneumonia show no special features. A study of Table 7 reveals that the complications in the present series of 500 Type III pneumonias occurred in about the usual incidence rate.

TABLE 7.—COMPLICATIONS IN PNEUMOCOCCUS TYPE III PNEUMONIA.

Complications.	No. of cases.	Incidence, %.	Died.	Fatality, %.
Empyema	28	5.6	13	46.4
Meningitis	4	0.8	4	100.0
Endocarditis	0	0	0	
Pericarditis	3	0.6	3	100.0
Arthritis	2	0.4	1	50.0
Phlebitis	2	0.4	1	50.0
Otitis*	10	2.0	0	
Cardiac irregularity	14	2.8	11	78.6
Delayed resolution	2	0.4	0	
Cellulitis	6	1.2	1	16.7
Lung abscess	1	0.2	1	100.0
Pleural effusion	7	1.4	5	71.4

* Eight of these cases were in children.

It was shown by Cecil, Baldwin and Larsen that Type I pneumonia is more frequently complicated by empyema than any of the other pneumococcal types. These investigators found that empyema occurred in almost 7% of their Type I cases. In the present series of Type III cases, empyema developed in 5.6% of the series, which is just about the usual incidence for empyema in pneumonia as a whole. Empyema was most common in bacteremic cases, as indicated in Table 8. Of the 8 bacteriemic patients who developed empyema, only 2 recovered, while of 6 non-bacteremic cases, 4 recovered.

TABLE 8.—INCIDENCE OF EMPYEMA IN BACTEREMIC AND NON-BACTEREMIC CASES.

	No. of cases.	Cases with empyema.	Incidence, %.	Death rate, %.
Bacteremic patients	55	8	14.5	75.0
Non-bacteremic patients	132	6	4.5	33.3

It is interesting to note the absence of endocarditis as a complication in Type III pneumonia in the present series. Blake encountered only 1 case of Type III endocarditis in his series of 111 cases. Necropsies on all our fatal cases would no doubt have revealed a terminal pneumococcal endocarditis in a few cases; but even admitting this source of error, the infrequence of endocardial involvement in Type III pneumonia is probably due to the relatively low incidence of bacteremia in Type III cases. Cecil and Plummer[12] found that the highest incidence of pneumococcal endocarditis was

in Type II pneumonia; in other words, in the type that shows the highest incidence of pneumococcal bacteremia. There appears to be a definite relationship between the incidence of bacteremia and the incidence of endocarditis as a complication.

Death Rate. It has already been shown (Table 6) that the death rate for this series of 500 cases of Type III pneumonia was 42.2%, a figure which agrees closely with that reported by other investigators (Blake, 44.3%; Cole, 43%; Bullowa, 40%). Finland and Sutliff, however, report a much higher rate in their series of 225 cases of Type III pneumonia (60%). In our experience, Type III pneumonia, fatal as it is, ranks second in virulence, being surpassed by a small margin by pneumococcus Type II pneumonia, with a death rate of 48.8%. Of the three dominant types, Type I has the lowest death rate—in our series, 28.2% for cases that received no serum. The figures for both Type I and Type II infections would be considerably lower for serum-treated cases. We have already pointed out how much higher the rate becomes for all three types when only bacteremic cases are considered. Type III cases with positive blood cultures had a death rate of 85.4%, which was almost three times higher than that for patients with negative cultures. Finland and Sutliff reported 100% mortality for their septic Type III series. It was also apparent in our group that as the age increased the tendency to bacteremia increased, and this may explain in part the high fatality rate in patients over 50 years.

Over a period of more than a decade there were 214 deaths from Type III pneumonia in Bellevue Hospital. Some of our Type III patients received antipneumococcal serum in various forms, but as it never appeared to have the slightest clinical effect, there is no reason to believe that its use affected the death rate in the Type III series in any way. During the same period there were 501 deaths from Type II and 222 deaths from Type I pneumonia. It is clear therefore that, although Type III pneumococcus is responsible for only 10 to 12% of all pneumococcal pneumonias, it contributes its share toward the death rate of pneumonia. It is interesting to analyze these deaths from pneumonia still further, particularly with reference to age, sex and chronic systemic disease.

Cecil, Baldwin and Larsen first called attention to the importance of age in the death rate of Type III pneumonia: Under 40 it is a comparatively mild infection, showing a death rate actually lower than in some other types; after 40 the death rate rises rapidly, but not more rapidly than that for Type II pneumonia. It has long been known, of course, that all types of pneumonia show a steadily increasing death rate for each decade. Apparently the reason for the high death rate in Type III pneumonia as a whole is that a very large proportion of Type III pneumonias occur in the later decades of life. The relation of age to mortality rate in Type III

pneumonia is shown graphically in Fig. 3. The curves for Type I and Type II pneumonias are included for comparison. From these curves it is clear that, as pointed out by Cecil, Baldwin and Larsen and corroborated by Blake, the death rate for Type III patients under 40 is little if any higher than that for Type I and Type II cases. After 40, the death rate for both Type II and Type III infections rises very rapidly, while in Type I cases the rise is more gradual.

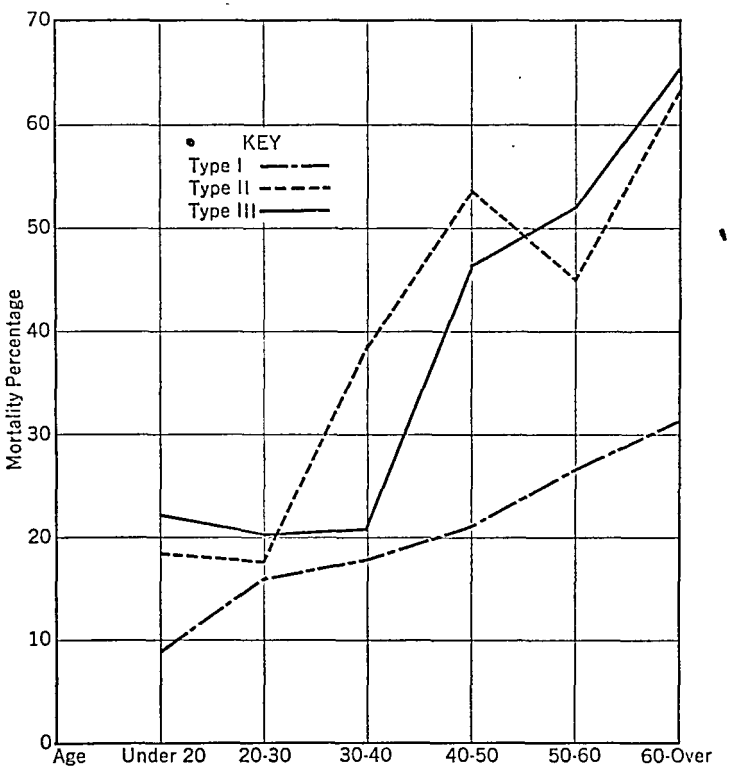


FIG. 3.—Mortality rates for pneumococcus Types I, II and III in relation to age.

In Table 9, it is surprising to note what a low percentage of the total deaths from pneumonia are caused by pneumococcus Type III in *males* under 50 (9.5%). On the other hand, in females under 50,

TABLE 9.—ANALYSIS OF TOTAL DEATHS FROM PNEUMONIA IN BELLEVUE HOSPITAL (1920–1932) WITH REFERENCE TO AGE AND SEX.

Type of pneumococcus	Males under 50 years.		Males over 50 years.		Females under 50 years.		Females over 50 years.	
	Deaths.	%.	Deaths.	%.	Deaths.	%.	Deaths.	%.
Type I . .	172	25.3	78	18.5	20	21.1	6	8.2
Type II . .	266	39.2	139	33.6	20	21.1	7	9.6
Type III . .	62	9.5	93	22.5	24	25.2	30	41.1
Misc. types .	177	26.0	105	25.4	31	32.6	30	41.1

Type III pneumonia was responsible for 25.2% of all deaths, and in females *over* 50, pneumococcus Type III wrought its greatest

havoc, causing 41.1% of all pneumonia deaths in this age-sex group. In this latter group, Type I and Type II pneumococcus played a comparatively insignificant rôle as a cause of death.

TABLE 10.—INCIDENCE AND DEATH RATE FOR PNEUMONIAS WITH AND WITHOUT SYSTEMIC DISEASE.

Pneumonia.	With systemic disease.	Death rate.
Type I	20.4	32.0
Type II	33.0	49.0
Type III	49.6	53.6

Pneumonia.	Without systemic disease.	Death rate.
Type I	79.6	18.5
Type II	67.0	41.9
Type III	50.4	32.1

As would be expected, the high frequency of chronic disease in Type III pneumonia adds greatly to the seriousness of the prognosis. For example, Cecil and his co-workers found the death rate for 48 Type III pneumonias not associated with chronic disease was only 8.5%, whereas in 83 cases that were associated with chronic disease the death rate was 66.4%. In Blake's series, where the association of Type III with chronic disease was high even in the young, 19 of the 32 patients between 20 and 50 years had some form of chronic disease. Of these 19, 12 died, while of the 13 in previous good health, only 2 died. In Table 10, the incidence and death rate of Type III cases associated with systemic disease is indicated. For comparative purposes the death rate for cases without systemic disease is also shown. It is evident from a study of these figures that Type III pneumonia is not more serious than other types when it attacks people who have previously enjoyed good health. It becomes serious, however, when it affects those afflicted with some chronic disease or those who have attained old age. As Blake well expresses it, "Pneumococcus Type III pneumonia is a highly fatal specific infectious disease, due in general not to a highly infectious organism that attacks and kills a healthy host, but rather to a debilitated or senescent host who succumbs to what is a relatively mild and uncommon infection in the young and vigorous."

Discussion. In the preceding paragraphs we have attempted to show that Type III pneumonia has certain very definite characteristics which distinguish it sharply from other types. These special characteristics are no doubt due to the inherent qualities of pneumococcus Type III. This organism was originally spoken of as the Streptococcus mucosus, but was finally classified, and rightly so, as a pneumococcus. Dochez and Avery were the first to designate it pneumococcus Type III. The most important investigations into the nature of Type III pneumococcus are those of Avery[15] and his co-workers who have brought out some very interesting facts concerning the polysaccharid which is contained in the capsule of pneumococcus Type III. This capsular polysaccharid which is often referred to as the "soluble specific substance" varies for each

type of pneumococcus and, in fact, determines the specificity of each type. In 1931, DuBos and Avery[16] reported the discovery of a motile spore-bearing pleomorphic bacillus which had been isolated from peet oil and which had the ability of decomposing the specific polysaccharid of Type III pneumococcus. This specific action on the polysaccharid is due to an endocellular enzyme generated by the pleomorphic bacillus. The enzyme can be extracted by autolysis of the bacterial cells. In sterile solution the enzyme has the same specific action as do the organisms from which it is derived, decomposing the capsular polysaccharid of Type III pneumococcus, but having no effect on the polysaccharid of other pneumococcal types. In a subsequent study Avery and DuBos[17] showed that the bacterial enzyme which decomposes the polysaccharid of Type III pneumococcus *in vitro* also destroys the capsules of the living organisms growing in media and in the animal body, and that potent preparations of this enzyme would protect mice against infection with virulent Type III pneumococcus. Furthermore, the enzyme was found to exert curative action in mice infected intraperitoneally with pneumococcus Type III, even when the enzyme was injected 12 to 18 hours after infection. Goodner and DuBos[18] were able to save rabbits infected intradermally with pneumococcus Type III by injecting the enzyme intravenously 24 hours after inoculation with the culture. They noted that the amount of enzyme necessary to bring about the recovery of the infected rabbit bears a definite relationship to the severity of the infection as gauged by the number of pneumococci present in the circulating blood. Finally, in a recent article, Avery and his co-workers have demonstrated clearly the therapeutic value of the specific enzyme upon experimental Type III pneumococcus pneumonia in monkeys. Treatment with the enzyme was followed by cessation of spread of the pneumonic lesion, sterilization of the blood and early recovery, except in animals in which the severity of the disease was extreme. These authors found that in monkeys, as in rabbits, the therapeutic value of the enzyme was directly proportional to the number of pneumococci present in the circulating blood of the infected animal.

These studies have great theoretic and practical importance. They open up an entirely new line of attack against pneumococcal infections in general, and they possess great practical importance because at the present time we have no satisfactory serum treatment for Type III infections. The writer was never able to save monkeys infected with lethal doses of Type III pneumococcus by the administration of Huntoon's pneumococcus antibody solution. Cecil and Larsen[19] showed that pneumococcus antibody solution, though it affected favorably the death rate in both Type I and Type II pneumonias, had no effect whatever on the death rate in Type III pneumonia. A few years later, Cecil and Sutliff[20] had similar results with Felton's concentrated antipneumococcus serum. On

the other hand, Watson and Cooper,[21] producing intradermal lesions and frequent bacteremia in rabbits by the intradermal inoculation of Type III pneumococci, found that such bacteremia was checked and the rabbits protected by suitable amounts of Type III concentrated antiserum given intravenously 24 hours after the infecting doses. Furthermore, they found that the amount of Type III antiserum necessary to protect rabbits inoculated intradermally with virulent Type III cultures was not appreciably greater than the amount of Type I antiserum required to protect against Type I. The inconsistency between the results obtained by Watson and Cooper on rabbits and those obtained by Cecil on monkeys is not so striking as might at first appear. The former workers used a serum which contained 1000 protection units per cc. against a stock Type III strain. The serums which we used for our monkey experiments and for the clinical studies on patients possessed a much lower potency.

The whole problem of controlling Type III pneumonia by prophylactic immunization or by the use of a highly efficient serum centers around the difficulty of stimulating a high titer of immune bodies by the injection of killed or living Type III pneumococci. For example, Cecil and Steffen[22] found that 3 subcutaneous injections of pneumococcus Type I or Type II vaccine would confer on monkeys a complete immunity against pneumococcal pneumonia of homologous types. However, 3 subcutaneous injections of pneumococcus Type III vaccine gave a complete protection against Type III pneumonia in only 4 out of 8 monkeys vaccinated. The same investigators did succeed in vaccinating monkeys against pneumococcus Type III pneumonia by giving Type III vaccine in large doses intratracheally. Ross[23] was able to protect rats against pneumococcus Type III pneumonia by feeding them Type III pneumococcus vaccine. Cecil and Austin,[24] studying the blood serum of 8 human volunteers who received a polyvalent pneumococcus vaccine subcutaneously, tested their serums 7 days later for agglutinins and protective bodies. A number of the vaccinated men developed agglutinins for Type I and Type II pneumococcus, but none for Type III. In a similar way, all of the men developed protective bodies against Type I and Type II pneumococcus, but only 3 of the 8 showed any protection against Type III.

One is justified in making the inference that immunity against Type III pneumococcus is difficult to acquire by either artificial or natural methods. The not unusual recurrence of Type III pneumonia in the same individual is another indication that this is true.

The treatment of pneumococcus Type III pneumonia with homologous convalescent serum has been tried by Beebe and Sutliff.[25] The patient was a male, aged 55, and he received his first injection of Type III convalescent serum (120 cc.) on the fourth day of his disease. On the fifth day he received 190 cc. of Type III convales-

cent serum. The Type III serum administered showed only slight protective power for mice, but had moderately high agglutinins and precipitin titers. In spite of the serum administered, the patient developed a positive blood culture and died on the sixth day of his disease. Barach treated 6 cases of pneumococcus Type III pneumonia by transfusing them with blood from donors who had been immunized against pneumococcus Type III. The serums employed all showed a fairly high titer of protective bodies as tested on mice. Four of the 6 patients had a Type III bacteremia, and all died. The 2 Type III cases with sterile blood cultures survived. According to Barach,[26] the immediate effect of the transfusion on the clinical condition of the patient was negligible.

Summary. 1. Pneumococcus Type III ranks third as an exciting agent in lobar pneumonia, causing 11.8% of all pneumococcal pneumonias. It is surpassed only by pneumococcus Type I and Type II in respect to prevalence.

2. The incidence of pneumococcus Type III pneumonia increases with age. In the present series pneumococcus Type III was responsible for 32.8% of all pneumococcal pneumonias that occurred after the age of 60.

3. Pneumococcus Type III pneumonia is relatively commoner in women than in men. The incidence rate for women is 18.2%, as compared with 11.6% for men. This is in sharp contrast to Type I and Type II infections, where the incidence per cent for the two latter types is considerably higher for males than for females.

4. Pneumococcus Type III pneumonia is very prone to occur in individuals who are already the victim of some chronic disease. In the present series of 500 cases, 49.9% of the patients were afflicted with some chronic malady. This association of chronic disease with pneumonia was much higher in Type III than in Type I or Type II infections.

5. Bacteremia was noted in 29.4% of the Type III patients who were subjected to blood cultures.

6. The death rate for the entire series of 500 cases of Type III pneumonia was 42.2%, a figure which agrees closely with that reported by other investigators. In Bellevue Hospital, however, Type III pneumonia ranks second in severity, being surpassed by pneumococcus Type II pneumonia with a death rate of 48.8%.

7. The death rate for Type III pneumonia was influenced by a number of factors. In bacteremic cases it was 85.4%. The death rate is much affected by age and the incidence of chronic systemic disease. In patients under 40 years the death rate was approximately 20%; over 60 years, 65.4%. In patients without systemic disease the death rate was 32.1%; with systemic disease, 53.6%.

8. There is no satisfactory serum therapy for pneumococcus Type III pneumonia at the present time. The most promising outlook with respect to a specific treatment for this infection is the

enzyme of Avery, which destroys the specific carbohydrate in the capsule of pneumococcus Type III, and which in the case of animals infected experimentally with lethal doses of Type III pneumococcus, has shown distinctly curative properties.

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STUDIES OF VITAMIN C EXCRETION AND SATURATION.*

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In 1933 Harris, Ray and Ward,[1] using Birch, Harris and Ray's[2] micromodification of Tillmans'[3] titration method for the determination of vitamin C found that normal human subjects excreted sig-

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nificant amounts of the vitamin in the urine.* The usual daily excretion was observed to be relatively constant (30 to 33 mg.). Well-nourished normal subjects were found to behave as though they had appreciable reserve "stores" of the vitamin, for when the vitamin was temporarily withheld from their diet they continued to excrete it for a time at an almost steady rate. When a large dose of the vitamin was given an increase in the urinary excretion was observed. These observations led them to believe that the urinary output was dependent both on the immediate intake and on the past nutritional history, that is to say, on the state of vitamin "saturation." In the same year von Eekelen, Emmerie, Josephy and Wolff[4] reported a series of "normal values" for 24-hour excretion similar to those of Harris, Ray and Ward.

Hess and Benjamin,[10] in 1934, studied the urinary excretion of the vitamin in children and were able to detect an appreciable excretion only when large amounts of vitamin C were fed. However, Harris and Ray[11] found the excretion of the vitamin by well-fed children to be of the same order as that of adults when expressed on a basis of body weight. Hess and Benjamin were led to conclude that the amount of vitamin C in the urine of children under normal dietary conditions is negligible, and when present in significant amounts represents an excess which appears after complete saturation of the tissues has occurred. We believe these conclusions are incorrect and that their subjects probably had a deficient store and a low intake of vitamin C. Rohmer, Sanders and Bezssonoff[12] found vitamin C in measurable quantities in the urine of infants. Infants of 5 months of age continued to excrete the vitamin when fed a diet low in vitamin C, but when older children were placed on a vitamin C-low diet the excretion of the vitamin fell to a low level.

Johnson and Zilva,[6] in 1934, studied the urinary excretion of vitamin C and were unable to find the relatively constant excretion observed by Harris, Ray and Ward.[1] They found that the usual daily output varied from 0 to 15 mg. in 3 subjects and from 80 to 150 mg. in the fourth. This variation was related to differences in the diets of the subjects tested. When average doses of 100 mg. daily were given to one subject on a low vitamin C diet, Johnson

* Although the substance reacting in urine with Tillmans' reduction indicator (2.6 dichlorophenol-indophenol) as the test is ordinarily performed has not been proven conclusively to be vitamin C (ascorbic acid), satisfactory evidence of its identity with the vitamin has been obtained through biologic assay by von Eekelen, Emmerie, Josephy and Wolff[5] and by Johnson and Zilva.[6] Recently Guerrant, Rasmussen and Dutcher[7] found that the amounts of vitamin C in fruit and vegetable juices as determined by the method of Tillmans compared closely with those determined by biologic assay. The specificity of the method for the determination of the vitamin in urine has also been investigated by Harris[8,9]. He concluded that no known constituent of urine was likely to interfere, provided the titration was carried out rapidly.

and Zilva found that no significant amounts were excreted in the urine until the 7th day. The output then gradually rose until the 17th day, after which it remained at a constant level of about 76% of the intake. They considered this subject saturated with vitamin C, and found that if now, after a lapse of 5 days, a dose of 180 mg. were given, 80% of it was returned in the urine. When unsaturated subjects were given larger doses they excreted about 60% by the 5th day, and maintained this level as long as the dose was continued. When the test dose was discontinued the urinary excretion of the vitamin quickly fell to the subject's usual level. Harris and Ray[11] similarly observed that when subjects on a vitamin C-free diet were given 140 mg. of vitamin C daily, there was very little increase in the urinary excretion of the vitamin. When 280 mg. of vitamin C were given daily the subject rapidly became saturated and after 6 days excreted 80% of the daily dose. When the administration of the vitamin was stopped, excretion quickly fell to a low level. Johnson and Zilva[6] concluded that there seemed to be "a definite capacity for 'saturation' which is independent of the dose" and Harris and Ray[11] that the state of saturation of the subject depends on the amount of vitamin C in the past diet.

Harris and Ray,[11] in their second paper, studied the excretion of vitamin C in a small group of children, some scorbutic, others presumably with a latent scurvy and the remainder normal. A few normal adults were also included. They found the children with scurvy to have very low excretions (0.4 to 0.7 mg. daily) and in them fairly large test doses of the vitamin failed to provoke any significant urinary excretion. After cure of the scurvy the daily excretion rose to 1.4 to 2.4 mg., and large test doses now produced a sharp rise in excretion. Subjects with latent scurvy and those with a definite history of dietary insufficiency also had fairly low excretions which suggested that such studies of urinary excretion might be of clinical value.

Early in 1935 Schroeder,[13] using a different method (iodometric titration), arrived at conclusions similar to those of Harris, Ray and Ward[1] and Johnson and Zilva[6] and found a normal daily excretion of 19 to 29 mg. Following test doses of 300 mg. of vitamin C there was a rise in the excretion of the vitamin.

Experimental. The purpose of our study was to determine the daily excretion and degree of "saturation" with vitamin C of subjects either patients of the clinic or persons of a similar social and economic class, whose diets were suspected of being deficient in various respects. For comparison a supposedly normal group made up of members of the staff was included. In addition we studied the excretion of vitamin C in 4 normal subjects over much longer periods and under varying conditions, with reference to the excretion of vitamin C following "saturation," the rate at which "sat-

uration" is lost and the effect of giving small amounts of vitamin C to subjects in the "saturated" and "non-saturated" states. Thirty-one subjects in all were studied, including 15 in the "patient" group, 9 members of the non-resident hospital staff and 7 members of the resident staff. All of the patients were ambulatory and at the time of the test were free of any significant complicating illness. In general, their diets were known to be low in protein, fresh fruits and milk. Though high in fresh vegetables, their habitual methods of cooking these in large quantities of fat for long periods of time may have lowered the initial vitamin C content. The non-resident hospital-staff group was composed of doctors, technicians and clerical workers whose diets were in no way uniform. Some were known to take fairly large amounts of vitamin C-containing foods, while others took rather small amounts, due to dietary preferences and dislikes. The third group, members of the resident staff, all ate in the hospital dining rooms, and were offered the same food. The diet was presumably well balanced, and differed individually only as their personal tastes differed. The 4 subjects who were studied over a longer period were from the non-resident staff group. Though their diets were believed in the beginning to be adequate, it is possible that in 3 of them the daily intake of vitamin C was rather small. After a preliminary period on their usual diet these 4 subjects were placed on a vitamin C-"free" diet for the subsequent period of the experiment.

The vitamin C content of the urine was determined by the use of Tillmans'[3] indicator, 2.6 dichlorophenol-indophenol, standardized every 3 days against a known solution of ascorbic acid. The micro technique described by Harris and Ray was used with few exceptions. The indicator was titrated from a micro-burette into an aliquot of acidified urine and the amount of ascorbic acid expressed in milligrams. Titrations were carried out quickly and the volume of the aliquot of urine was varied inversely with the amount of ascorbic acid it was expected to contain. When possible, the specimens were titrated as soon as voided. When this was impractical, about 10% 2N sulphuric acid was used as a preservative. In all the tests of daily excretion 2 or more 24-hour determinations were carried out, and the figures for daily excretion represent an average of these determinations. Tests of "saturation" consisted in determining the per cent of a test dose (usually about 600 mg.) excreted in the urine in the 24 hours during which this amount was given. The coöperation of the subjects was excellent and we feel certain that all the urine was obtained. In all the experiments in which vitamin C was given, fresh orange juice was used as the source, the ascorbic acid content being determined by titration as described above. All of the experiments were carried out during the winter and early spring months.

Results. The results of the tests of daily excretion are shown in Table 1. In the patient group the daily excretion ranged from

TABLE 1.—THE DAILY (24 HOUR) URINARY EXCRETION OF VITAMIN C (ASCORBIC ACID).*

Patient group.		Resident staff.		Non-resident staff.	
Subject.	Vitamin C, mg.	Subject.	Vitamin C, mg.	Subject.	Vitamin C, mg.
F. G.	7.5	C. T.	12.2	H. F.	10.7
F. W.	9.0	R. B.	12.3	E. W.	14.9
H. K.	10.0	W. F.	12.9	J. A.	15.5
R. J.	12.0	R. T.	15.1	J. Y.	20.1
V. C.	13.0	A. W.	16.0	F. B.	22.3
L. F.	14.2	M. M.	23.3	A. B.	30.8
C. S.	15.0	M. G.	24.5	M. C.	43.0
W. J.	16.0			F. R.	64.2
C. J.	16.0			M. D.	80.1
K. S.	17.5				
E. M.	18.5				
A. R.	19.0				
A. J.	22.0				
J. N.	23.0				
H. S.	34.0				

* In each group the values are arranged in ascending order.

TABLE 2.—RETENTION AND EXCRETION OF TEST DOSE OF VITAMIN C (ASCORBIC ACID).

Subject.	Test dose, mg.	Excretion.		Apparent retention.	
		Mg.	%.	Mg.	%.
Patient group:					
F. W.	600	13.7	2.3	586.3	97.7
R. J.	493	15.8	3.2	477.2	96.8
H. K.	493	18.4	3.7	454.6	96.3
E. M.	784	32.5	4.1	751.5	95.9
J. N.	425	17.6	4.1	407.4	95.9
H. S.	637	31.3	4.9	605.7	95.1
C. S.	414	20.4	4.9	393.6	95.1
W. J.	417	22.9	5.5	394.1	95.5
L. F.	395	31.1	7.9	363.9	92.1
F. G.	636	56.4	8.9	579.6	91.1
C. J.	634	73.8	11.6	560.2	88.4
V. C.	654	88.2	13.5	565.8	86.5
A. R.	493	124.0	26.0	369.0	74.0
A. J.	493	172.0	34.9	321.0	65.1
Resident staff:					
A. W.	633	11.4	1.8	621.6	98.2
R. T.	594	20.5	3.5	573.5	96.5
C. T.	706	28.7	4.1	677.3	95.1
R. B.	706	38.2	5.4	667.8	94.6
W. F.	706	44.0	6.2	668.0	93.8
M. G.	654	223.0	32.3	468.0	67.7
M. M.	646	239.0	37.0	407.0	63.0
Non-resident staff:					
J. Y.	288.7	22.1	7.7	266.6	92.3
J. A.	420	64.1	15.3	355.9	84.7
H. F.	968	167.2	17.3	800.8	82.7
E. W.	586	207.0	35.3	379.0	64.7
M. D.	312	193.7	62.7	118.3	37.3
M. C.	352	240.0	68.2	112.0	31.8
F. R.	573	557.0	97.2	16.0	2.8

7.5 to 34 mg., 12 of the 15 subjects excreting less than 20 mg. Among the resident staff group the excretion varied between 12 and 24.5 mg., only 2 showing an excretion above 20 mg. Both of these subjects are dietitians. The non-resident staff group excreted from 5 to 80 mg. and 6 of the 9 showed an excretion of 20 mg. or more.

TABLE 3.—EXCRETION OF VITAMIN C AFTER SATURATION. SUBJECTS ON VITAMIN C-"FREE" DIET.

Subject.	Days.	Test dose, mg.	Excretion. Mg.	Excretion. %.
M. C.	1	...	38.4	
	2	600	311.4	51.9
	3	600	539.0	89.9
	4	...	254.1	
	5	...	59.3	
	6	600	444.3	75.2
	7	...	57.6	
	8	...	36.8	
	9	...	38.5	
	10	...	34.0	
	11	...	21.4	
J. Y.	1	...	38.9	
	2	600	378.5	63.1
	3	600	382.8	64.8
	4	600	429.8	71.6
	5	600	596.2	99.4
	6	...	131.0	
	7	...	46.4	
	8	...	39.2	
	9	...	45.4	
	10	...	36.8	
	11	...	39.7	
	12	...	40.7	
	13	...	28.7	
	14	...	19.5	
J. A.	1	600	497.4	79.6
	2	600	581.0	96.8
	3	...	112.2	
	4	...	76.4	
	5	...	48.0	
	6	600	422.0	70.4
	7	600	586.8	97.8
	8	...	68.8	
H. F.	1	...	32.7	
	2	600	425.2	70.9
	3	600	367.0	61.2
	4	600	396.7	66.3
	5	600	211.3	35.2
	6	600	Lost specimen	
	7	600	556.0	94.3
	8	...	107.4	
	9	...	45.0	
	10	...	32.0	
	11	...	26.6	
	12	...	17.7	
	13	...	19.4	
	14	...	18.1	
	15	...	13.1	

The results of the saturation tests are shown in Table 2. In the patient group 2.3 to 34.9% of the test dose was excreted, or, more

significantly perhaps, 65.1 to 97.7% of the dose was apparently retained. Of the 15 subjects, 13 excreted a very small part of the amount given. All of them were subjects who had shown a low daily excretion. The one subject who had a fairly high daily excretion excreted a considerable part of the test dose. Among the resident staff group the excretion of the test dose varied from 1.8 to 37%. Only the 2 subjects with the higher daily excretion excreted more than 30% of the test dose. In the non-resident staff group the excretion of the test dose ranged from 7.6 to 97.2%. The majority of the subjects in this group excreted a considerable percentage of the test dose and had shown a relatively high daily excretion. Those who excreted smaller amounts of the test dose were the ones who had had a smaller daily excretion.

TABLE 4.—EXCRETION OF VITAMIN C AFTER SATURATION.
SUBJECTS ON USUAL DIET.

Subject.	Days.	Test dose, mg.	Excretion.	
			Mg.	%.
M. C.	1	...	45.3	
	2	352.6	240.1	68.2
	3	378.3	325.1	82.7
	4	...	146.4	
	5	...	186.8	
	6	...	88.6	
	7	...	72.0	
	8	...	82.8	
J. Y.	1	...	15.0	
	2	288.7	22.1	7.7
	3	420.0	146.1	34.8
	4	395.5	271.4	54.8
	5	691.0	579.0	84.0
	6			
	7	...	56.5	
	8	...	51.8	
	9	...	48.3	
J. A.	1	...	13.8	
	2	420.0	64.1	15.3
	3	592.5	533.6	90.0
	4	656.0	525.8	80.0
	5	...	82.5	
	6	...	62.8	
	7	...	39.4	
H. F.	1	600.0	258.0	43.0
	2	600.0	549.6	91.5
	3	...	38.9	
	4	...	32.7	
	5	600.0	425.2	70.9

Certain of the data obtained from the study of 4 subjects over a much longer period of time are shown in the remaining tables. When the subjects were maintained on a vitamin C-"free" diet following "saturation," the daily excretion was observed to fall rapidly to a low level (Table 3). Thus, Subject H. F., who excreted 556 mg. on the 6th and last day of "saturation," excreted 107.4 mg. on the 1st and 45 and 32 mg. on the 2d and 3d days thereafter, respectively. By the 8th day the excretion had fallen to 13.1 mg.,

an amount which was about equal to the daily excretion on her normal diet and comparable to that found in subjects suspected of an inadequate intake of the vitamin. All the subjects on a vitamin C-"free" diet showed a gradual but steady decrease in daily excretion at a rate which varied in the individual subjects but presumably would eventually have reduced excretion to subnormal levels in all the subjects, had the experiment continued long enough.

TABLE 5.—THE VITAMIN C EXCRETION OF "SATURATED" SUBJECTS, GIVEN AMOUNTS OF THE VITAMIN COMPARABLE TO THOSE TAKEN IN A GOOD DIET,* WHILE MAINTAINED ON A VITAMIN C-"FREE" DIET.
(Comparison With the Excretion of the Same Subjects After Saturation, While on Their Usual Diet.)

		Vitamin C-free diet.			Usual diet.		
			Vitamin C excretion.			Vitamin C excretion.	
Subject.	Days.	Vitamin C intake, mg.	Mg.	%.	Vitamin C intake, mg.	Mg.	%.
M. C. . .	1	1,000	389.8	39.0			
	2	1,000	539.1	53.9			
	3	930	841.1	90.2	352.6	240.1	68.2
	4	1,000	1,059.0	160.0	378.3	325.1	82.7
	5	..	222.0	...	...	146.4	
	6	75	72.0	96.4	...	186.8	
	7	75	85.2	113.5	...	88.6	
	8	75	86.9	115.8	...	72.0	
	9	50	...	...	...	82.8	
	10	75	82.0	109.4			
J. Y. . .	1	600	150.5	25.8			
	2	600	344.3	57.4	288.7	22.1	7.7
	3	600	586.4	98.1	420.0	146.1	34.8
	4	300	307.1	102.3	395.5	271.4	54.8
	5	1,000	878.8	87.9	691.0	579.0	84.0
	6	..	173.4				
	7	100	90.6	90.6	...	56.5	
	8	100	117.5	117.5	...	51.8	
	9	100	204.5	204.5	...	48.3	
	10	..	43.3				
	11	100	51.8	51.8			
	12	100	116.1	116.1			
H. F. . .	1	1,000	508.1	50.8			
	2	1,000	690.5	69.1			
	3	1,011	773.6	76.5			
	4	1,000	511.5	51.2			
	5	747.3	344.4	45.1	600.0	258.0	43.0
	6	1,000	941.8	94.2	600.0	549.6	91.5
	7	50	151.4	303.0	...	38.9	
	8	50	116.3	232.4	...	32.7	
	9	50	58.6	117.7			
	10	50	80.6	160.9			
	11	50	71.9	143.6			
	12	76					
	13	50	53.9	107.8			

* These subjects were kept on an otherwise vitamin C-free diet.

With the subjects on their usual diet, the decrease in daily excretion after "saturation" corresponds roughly to the nature of the individual diets. In those subjects whose usual diet contained a considerable amount of vitamin C, the decrease, though rapid, was

not as great as when on the vitamin C-"free" diet. Thus, Subject M. C. on his usual diet excreted 82.8 mg. on the 5th day following "saturation" (Table 4). During a similar test when on a vitamin C-"free" diet, the excretion on the 5th day was 21.4 mg. (Table 3). Subject J. Y., whose usual diet was believed to be rather low in

TABLE 6.—RESATURATION TESTS WITH VITAMIN C AT VARYING INTERVALS. SUBJECTS ON VITAMIN C-"FREE" DIET.

Subject.	Days.	Test dose, mg.	Excretion. Mg.	Excretion. %.
M. C.	1	600	378.6	63.1
	2	600	517.2	86.2
	3	...	156.5	
	4	...	65.2	
	5			
	6			
	7			
	8	...	42.3	
	9	...	38.4	
	10	600	311.4	51.9
	11	600	509.3	84.8
	12	...	143.5	
	13	...	53.2	
	14	...	30.3	
	15	600	293.1	48.8
	16	600	392.2	65.4
	17	600	539.0	89.9
	18	...	254.1	
	19	...	59.3	
	20	600	444.3	75.2
J. Y.	1	600	120.2	20.3
	2	600	469.9	78.3
	3	600	474.9	79.1
	4	600	542.6	90.5
	5	...	123.3	
	6	...	77.1	
	7	...	33.9	
	8	...	38.8	
	9	600	378.5	63.0
	10	600	382.8	64.8
	11	600	429.8	71.6
	12	600	596.2	99.4
J. A.	1	600	587.3	97.9
	2	600	594.3	99.1
	3	600	625.5	104.2
	4	600	621.7	103.6
	5	600	582.7	97.2
	6	600	586.1	97.7
	7	600	477.4	79.6
	8	600	581.0	96.8
	9	...	112.2	
	10	...	76.4	
	11	...	74.9	
	12	600	422.5	70.4
	13	600	586.0	97.8

vitamin C, when on that diet excreted 48.3 mg. on the 4th day. When on a vitamin C-"free" diet after "saturation," the excretion on the 4th day was 45.4 mg. (Tables 3 and 4).

When known amounts of vitamin C, comparable to those which

might be taken in a "good" diet (50 to 100 mg.), were given to the subjects on a vitamin C-"free" diet following "saturation," the daily excretion was not only greater than when no vitamin was given but was higher than when the subject was continued on his usual diet.

"Resaturation" tests at varying intervals showed that "saturation" is quickly lost when the individual is on a vitamin C-"free" diet (Table 6). In as short a time as 2 days "saturation" may be lost and a "resaturation" test may show as much as 25% retention of the test dose (Subject M. C.). Some subjects even on their usual diet appear to lose their "saturation" quickly (Table 4). When, however, 50 to 100 mg. per day were given following "saturation," the "saturation" was apparently maintained for some time (Table 5).

TABLE 7.—EXCRETION OF VITAMIN C BY UNSATURATED SUBJECTS DURING ADMINISTRATION OF SMALL, VARYING AMOUNTS OF VITAMIN C. SUBJECTS ON VITAMIN C-"FREE" DIET.

Subject.	Days.	Test dose, mg.	Excretion, mg.
M. C.	1	...	36.8
	2	...	38.5
	3		34.0
	4	...	21.4
	5	...	32.8
	6	..	39.4
	7	25	32.6
	8	50	36.3
	9	100	39.8
J. Y.	1	...	28.7
	2	.	19.5
	3	.	31.5
	4	..	27.2
	5		24.5
	6	25	25.3
	7	50	24.9
	8	75	25.5

The intake of small but varying amounts of vitamin C (25 to 100 mg.) by "unsaturated" subjects on a vitamin C-"free" diet did not affect the daily excretion significantly (Table 7). Thus Subject J. Y., whose daily excretion for 5 days preceding the test ranged from 19.5 to 31.5 mg., excreted 24.9 to 25.5 mg. daily during the 3 days on which he was given 25, 50 and 75 mg., respectively. In contrast, in the saturated state, the administration of 100 mg. was immediately reflected in the urinary excretion (Table 5).

When comparison is made between the amounts of vitamin C excreted following nearly complete saturation (with the subject on a vitamin C-"free" diet) and the amounts retained at the next subsequent saturation, a considerable discrepancy is found and the amounts which were required to "resaturate" are found to be considerably greater than the amounts which had been excreted in the interval (Table 8). In nearly every period of this kind in which suitable data were available, this discrepancy was observed. Dif-

TABLE 8.—COMPARISON BETWEEN THE AMOUNTS OF VITAMIN C EXCRETED FOLLOWING NEARLY COMPLETE SATURATION AND THE AMOUNTS RETAINED AT THE NEXT SUBSEQUENT SATURATION. SUBJECTS ON VITAMIN C-"FREE" DIET.

Subject.	Days.	Vitamin C intake, mg.	Vitamin C excretion in urine, mg.	Apparent retention, mg.		
M. C. . . .	1	600	311.4			
	2	600	509.3			
	3	...	143.5			
	4	...	53.2		Total excretion (urine)	227.0 mg.
	5	...	30.3			
	6	600	293.1	306.9		
	7	600	392.2	207.8	Total apparent retention	575.7 mg.
	8	600	539.0	61.0		
					Unaccounted for in urine	348.7 mg.
H. F. . . .	1	600	556.0			
	2	...	107.4			
	3	..	45.6			
	4	. .	32.2			
	5	...	26.6			
	6	.	17.7		Total excretion (urine)	294.7 mg.
	7	...	19.5			
	8	...	18.0			
	9	...	13.1			
	10	.	14.7			
	11	1,000	508.1	492.0		
	12	1,000	690.5	309.5		
	13	1,010.8	773.6	237.2	Total apparent retention	1,988.3 mg.
	14	1,000	511.5	488.5		
	15	747 3	344.4	402.9		
	16	1,000	941.8	58.2		
					Unaccounted for in urine	1,693.6 mg.
J. Y. . . .	1	600	542.6			
	2	...	123.3			
	3	...	77.1		Total excretion (urine)	273.2 mg.
	4	...	33.9			
(First period)	5	...	38.9			
	6	600	378.5	221.5		
	7	600	387.8	217.2	Total apparent retention	612.7 mg.
	8	600	429.8	170.2		
	9	600	596.2	3.8		
					Unaccounted for in urine	339.5 mg.
	1	600	596.2			
	2	...	131.0			
	3	...	46.4			
	4	...	39.2			
	5	. .	45.4			
	6	...	36.8			
	7	...	39.7			
	8	...	40.7		Total excretion (urine)	540.6 mg.
(Second	9	. .	28.7			
period)	10	...	19.5			
	11	...	31.5			
	12	.	30.0			
	13	. .	27.2			
	14	. .	24.5			
	15	25	25.3			
	16	50	24.9	25.1		
	17	75	25.5	49.5	Total apparent retention	793.4 mg.
	18	600	150.5	449.5		
	19	600	344.3	255.7		
	20	600	586.4	13.6		
					Unaccounted for in urine	252.8 mg.

ferences in the amount of the vitamin unaccounted for in the urine were found among the different subjects and in the same subject at different times. When the amounts are computed on a daily basis the same differences are found.

Discussion. Although the values for the daily excretion vary widely, they correspond to the probable differences in vitamin C intake of the different groups and the individual subjects. Thus, the lowest values generally were found among the patient group whose diets as a group were undoubtedly lowest in vitamin C. Even the surprisingly low excretion of most of the resident staff group seems adequately explained by a dietary preference which limited the intake of vitamin C-containing foods in spite of the provision of an adequate diet. Individual variations are similarly explained. For example, the 2 subjects with the highest excretions in the non-resident staff group were found to be taking unusually large amounts of the vitamin.

Any conclusions regarding the "normal" daily excretion are made difficult by the lack of knowledge of the effect and manifestations of a slight deficiency of vitamin C and ignorance as to the optimal intake. The results of other investigators show an even wider range than ours, from 0 to 150 mg. (Johnson and Zilva). There is reason to believe, however, that in some of the studies reported, the diets of the subjects showing the low daily excretions were to some degree deficient.[6,10] In our study, the patient group, most of whom had a small excretion, were drawn from a class in whom manifestations of a mild scurvy have been observed and a few of the subjects themselves had had suspicious symptoms in the past. Disregarding those in the supposedly normal group whose diet was found to be questionable and taking those whose diets appeared reasonably adequate, the daily excretion of vitamin C was found to be in the neighborhood of 20 to 80 mg., values which correspond fairly well to those of Harris and Ray. On this basis we have tentatively adopted an excretion of 20 mg. per day as the lower normal limit of excretion in adults.

Some additional evidence respecting the normal daily excretion is obtained from the extended study of the 4 normal subjects. When amounts of vitamin C which roughly correspond to those taken in a "good" diet were given to nearly "saturated" subjects on a vitamin C-"free" diet, the daily excretion was maintained at a level somewhat above the general level of the subjects on the "better" diets and at a higher level than these same subjects excreted in an "unsaturated" state on their usual diet.

The results of the "saturation" tests show the same relationship to the probable intake of vitamin C as do the tests of daily excretion, and correspond roughly to the latter. It should be emphasized that "saturation" (80 to 100% of a test dose) in all probability

does not reflect an optimum or normal store of vitamin C in the body but is an artificial state which can be created only by the intake of excessive amounts of the vitamin. This conclusion is supported by the rapidity with which such a state is lost when the intake of large amounts is stopped (Table 3), as well as by the fact that only one subject in the group whose diets were considered to be adequate had an excretion even approaching 80% of the test dose. With our present knowledge it is impossible to define the normal degree of "saturation." While it is unlikely that the normal state is represented by an excretion of 80 to 100% of a test dose (about 600 mg. in adults), it seems probable that a return as low as 20% or less of such an amount reflects a suboptimal store of vitamin C. An excretion less than 20% (usually much less) of such a test dose was found in nearly all of the patient group and in several others whose diets were found to be at least questionably inadequate and whose daily excretion was low. Among those whose diets were considered reasonably adequate and who had the higher daily excretions, usually more than 30% of the test dose was excreted. For these reasons it is tenatively concluded that under normal conditions at least 30% of the test dose of the size we have used should be excreted. The fact that a few subjects whose daily excretion was above 20 mg. excreted less than 30% of the test dose may mean that a "normal" excretion may be maintained in the presence of an inadequate store.

The very great and abrupt reduction in daily excretion in a "saturated" subject when the intake of the vitamin is stopped (Table 3) suggests that the urinary excretion is regulated by the daily metabolism and is not merely an indication of an excess of the vitamin, as suggested by Hess and Benjamin.[10] Rather there appears to be a true storage with the controlled release of such amounts as are needed. There is some indication from our results that, in the absence of continued ingestion of vitamin C, this daily excretion, and presumably the amount used daily, gradually lessens as the store decreases until finally with the depletion of the reserve and the onset of scurvy the excretion becomes negligible. It cannot as yet be determined to what extent the rate at which daily excretion decreases depends on differences in the amount of vitamin required (or used). The fact that some vitamin continues to be excreted in spite of a dwindling reserve suggests that a circulating supply is maintained as long as possible, a certain amount of which is lost through kidneys which have no threshold for the excretion of this substance. If such an explanation is correct, the daily excretion is a true index of the amount of the vitamin which is being used by the body and of the adequacy of the supply, provided that the daily excretion is not sufficiently affected by other factors as to create a false impression. Two such possible factors are varia-

tions in the amount metabolized daily and in the daily intake. It is true that successive determinations may show variations in output with the subjects on their customary diet. However, in our experience these variations rarely exceed a few milligrams and the values of the daily excretion follow closely the usual trend of the individual subject. Also according to our results it seems unlikely that these variations are due to differences in intake, if the latter are in the neighborhood of amounts which might be contained in an ordinary diet and if the individual is not saturated or nearly saturated (Table 7). It appears that in the unsaturated subject any amount beyond that which may be needed for immediate use is stored and does not affect the daily excretion. Therefore, the daily fluctuations which are observed are probably the result of metabolic or similar factors and do not affect the value of the daily excretion as an index of the amount of vitamin C stored and used by the body.

Evidence of destruction of vitamin C within the body or its excretion by other channels is found in the discrepancy between the amount which is retained on a resaturation and the amount excreted in the urine in the period following the previous saturation (Table 8). In most instances the amount retained on a resaturation was considerably greater than that which had been lost in the urine following the previous saturation. At the present time no information is available as to the fate of this unaccounted-for portion. In the absence of other channels of excretion, variations in this fraction may be related to differences in requirements of different individuals or to variations in the same individual under different conditions.

Summary and Conclusions. Of 15 subjects whose diets were suspected of being inadequate in vitamin C, 12 excreted less than 20 mg. of the vitamin in the urine daily. Of 16 normal control subjects whose diets supposedly were adequate, 8 also excreted less than 20 mg. In the latter group subsequent inquiry suggested a limited intake, for one or another reason, of vitamin C among those with the low daily excretions.

Of the 31 subjects, 21 excreted but a very small part of a large test dose of the vitamin in the 24 hours during which it was administered, indicating an apparent retention of a large amount and suggesting a small store in the body. In general the tests of "saturation" corresponded to the tests of daily excretion and the probable dietary intake of the vitamin.

In 4 normal subjects it was found that: (1) Following "saturation" the urinary excretion of vitamin C quickly fell to a low level when the subject was kept on a vitamin C-"free" diet. On the "usual" diet the fall was nearly as great and as rapid.

2. With the subjects on their usual diet or a vitamin C-"free" diet, "saturation" was quickly lost when the administration of

vitamin C was stopped, "resaturation" tests at intervals of 2 to 3 days showing an apparent retention of as much as 25% of a test dose.

3. The administration of small but varied (25 to 100 mg.) doses of vitamin C to "unsaturated" subjects had little effect on the daily urinary excretion.

4. With the subjects on a vitamin C-"free" diet, the amount of the vitamin excreted in the urine in any given period following "saturation" is usually much less than the amount required to "resaturate."

5. For the present, a daily urinary excretion of vitamin C of 20 mg. and an excretion of 30% of a test dose (about 600 mg. in adults) is suggested as the lower limits of normal daily excretion and of "saturation" respectively.

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CLINICAL OBSERVATIONS ON PULMONARY BLOOD FLOW IN SILICOSIS AND OTHER FIBROTIC CONDITIONS OF THE LUNGS.*

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Connective tissue proliferation assumes a predominant rôle in many pulmonary diseases, and yet in the presence of such extensive anatomic changes the physiologic processes of the lungs often appear to go on practically unimpaired. This seems to us attributable to, at least, two important circumstances: (1) The velocity of blood flow in the lungs remains normal, and (2) the function of the alveolar capillary wall is practically undisturbed. In a sense, therefore, the widespread fibrosis of silicosis or of tuberculosis, lues or carcinoma represents an extravascular condition of the lungs and, with notable exceptions, does not assail the capillary alveolar bed. In silicosis, as we shall see, fibrosis from the start is diffuse and throughout the capillary alveolar bed, reaching the parenchyma only later.

In this report we shall deal with studies in pulmonary blood flow in silicosis and in other pulmonary fibrotic states, describing methods and discussing briefly the type of fibrosis encountered and recording our results on blood velocity. Other aspects, among them studies in blood gases, will be left for a later publication.

Methods. We employed two procedures: (*a*) The crude pulmonary circulation time,[1] or the arm to tongue circulation time devised by Winternitz, Deutsch and Brüll,[2] who utilized the bitter tasting property of sodium dehydrocholate (decholin) (first employed by Neubauer[3]) for measuring the arrival of its bitter taste after intravenous administration. Fishberg, Hitzig and King[4] later substituted glusid (saccharin) for decholin. In healthy individuals the average time for the completion of the pulmonary circuit is about 16 to 18 seconds, covering the pulmonary arterial and pulmonary venous channels.

(*b*) As an adjunct to the above the ether time method was also utilized.[5,6] This represents the time consumed for the odor of ether (3 cc. of 10% ether in normal saline solution) to reach the breath after its introduction into an elbow vein. The average time in healthy individuals for the completion of this pulmonary arterial circuit is about 5 to 9 seconds. Subtracting this result from the larger figure, *i. e.*, 16 to 18 seconds, for the entire pulmonary circuit we obtain a difference of about 8 to 10 seconds and this may be accepted as a fairly reliable measurement in time of the velocity of blood in the pulmonary venous circuit.

At the outset we must state that the saccharin or taste time and the ether or odor time were normal in practically all conditions and circumstances of pulmonary disease with the following notable

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exceptions: (*a*) When congestive heart failure was an accompanying or concomitant manifestation; (*b*) when myxedema was present, as after thyroidectomy for the relief of congestive failure (here the pulmonary circulation in both the arterial and venous system was slowed even after congestive failure had apparently subsided); (*c*) and in cases where we had good clinical ground for postulating the existence of pulmonary hypertension associated either with mitral valve disease or advanced emphysema; (here the ether time in some instances was prolonged to 12 to 18 seconds). A study of these latter cases will form the subject of a future communication in which observations on blood gas analysis correlated with probable derangements of the function of the alveolar membrane will be set forth. In passing, however, we may indicate at this point that we have reason to believe that increased ether figures represent an alteration in the membrane's capacity to diffuse gases through the alveolar membrane and are not due to any interference with the velocity in the pulmonary arterial circuit.

Retardation in blood velocity was confined primarily, if not wholly, to the pulmonary venous vessels and went hand in hand with congestive heart failure. In other words, *congestive heart failure is a phenomenon of disturbance of blood velocity, occurring primarily and from the very beginning in the venous system of the lungs.**

Fibrosis of the Lungs. With these tests many fibrotic pulmonary conditions were studied. Generally speaking, the fibrotic process in tuberculosis, lues, carcinoma, chronic infections, etc., presents scattered patchy connective tissue proliferations as a reactive response to the etiologic process in the areas affected. The changes take place throughout the parenchyma and secondarily extend to the pleura, mediastinum, diaphragm, etc.; the process is not centrifugal, the vast capillary alveolar bed remaining untouched essentially.

Thus, in tuberculosis neutrophils appear early in the formation of the tubercle and disappear at the stage of caseation, mononuclear and lymphocytic cells then taking over the phagocytosis of the débris. Fibrosis develops around the tubercle and also around cavities, but the fibrotic process fails to encroach upon the alveolar bed as a whole, however much it may involve isolated patches of alveoli. There are also some gross differences in the type of fibrosis seen here, as contrasted with silicosis; for example, the characteristic broad fibrotic apical and basal bands seen in tuberculosis and their tendency to be lateral and oblique as against the fibrotic strands in silicosis more longitudinal in direction and often characteristically

* On this point and related matters see: Miller, H. R.: The Rôle of the Lesser Circulation in Diseases of the Heart and Lungs, read December 7, 1934, at the Fiftieth Anniversary of the Founding of the Montefiore Hospital, New York City. See also: Hitzig, W. M., King, F. H., and Fishberg, A. M.: Arch. Int. Med., **55**, 112, 1935.

"tenting" the diaphragm. This brief description of fibrosis in tuberculosis holds also for syphilis and for carcinoma,* although in syphilis a greater production of perivascular fibrosis occurs as a consequence of the specific vascular-wall necrosis associated with this disease. In advanced and widely spread pulmonary tuberculosis the pulmonary blood velocity remained normal.

TABLE 1.—TUBERCULOSIS. NORMAL PULMONARY BLOOD VELOCITY IN 10 CASES OF ADVANCED PHTHISIS (SPUTUM POSITIVE) (FROM THE SEA VIEW HOSPITAL.)

Name.	No.	Age.	I. Ether time: velocity in pulm. arterial circuit. Seconds.	II. Saccharin time: velocity in entire(crude) pulm. circulation. Seconds.	III. Difference between II and I: velocity in pulm. venous circuit. Seconds.
T. G. . .	10202	67	5.00	15.5	10.50
H. L. . .	5161	38	7.00	12.5	5.50
S. G. . .	4949	59	6 50	17.0	10.50
C. M. . .	11512	43	7.25	14.0	6.75
G. F. . .	11676	58	6 00	13.5	7.50
S. G. . .	11760	32	5.50	16.0	10.50
M. N. . .	5866	60	6.00	15.0	9.00
W. Mc. .	4930	46	5 50	16.0	10.50
G. R. . .	8114	44	7 50	15.0	7.50
N. M. . .	9893	59	7.00	13.5	6.50

Quite different is the diffuse or centrifugal type of fibrosis involving the extensive alveolar capillary bed but leaving the parenchyma practically free; this is seen in extensive emphysema (primary or secondary), also in silicosis where the fibrotic thickening assails the fine lymphatic channels in the early stages and only much later and after prolonged silica exposure produces massive parenchymal alterations as well.

Silicosis, *par excellence*, is a fibrotic process. In the early stage phagocytosis is prominent, but even here connective tissue proliferation is to the fore early and continues long after the phagocytic activity subsides. Fibrotic thickening in the lymphatic channels ensues, the so-called perilymphatic nodulation appears at points of lymphatic vessel bifurcation and also where the lymphatics are crossed by bloodvessels or bronchial branches; the draining lymph nodes enlarge, mainly, the tracheobronchial group.

Up to this stage of perilymphatic nodulation restitution to normal is still possible, if no further exposure to silica dust takes place, and the stasis of silica dust and dust-laden phagocytes can leave the lymphatic channels free and clear.[7,8,9] The patient, in all probability, will then escape the further advances of the silica process, and from the point of view of compensation and insurance his condition will not be considered compensable.

* The table of figures in pulmonary carcinoma, for the sake of brevity, has been omitted; the results were within normal limits. No cases of pulmonary lues came to our attention.

With increased or continued exposure, however, to silica dust, perilymphatic nodulation, namely fibrosis and beading, will grow more marked. These beadings are the pseudotubercles of Mavrogordato (1922), the intralymphatic plaques of Carlton[10] (1924), and they are readily recognized in the Roentgen ray film. The lung parenchyma is not involved at this time, the lymphatic channels bearing the brunt of the change and exhibiting fibrotic thickening; this stage of the disease has been aptly termed by Mavrogordato "lymphatic cirrhosis." From the point of view of compensation in law, etc., these linear lymphatic thickenings and beading are looked upon as proof of pneumoconiosis, although the interparenchymatous lesions, *i. e.*, nodules, regarded as specific for silicosis, are not yet in existence. (According to Watkins-Pitchford,[11] the silicotic lesion is recognized in law only when it is visible and *palpable* in the lungs.) Under prolonged silica exposure these specific nodules eventually appear; they arise in the interstitial tissues of the parenchyma and not always or necessarily in relation to lymphatic tissues already involved. Occurring singly they may remain at about 1 mm. in diameter or else large massive induration takes place at the expense of the lung parenchyma; these parenchymatous lesions consist of dense connective tissue growth and are singularly free of cell elements.

Part and parcel of the silicosis picture is the frequent extensive emphysema surrounding areas of parenchymatous lesions and often forming characteristic cushions of emphysema at the apex and subapical regions; quite characteristic also is the occurrence of fibrotic strands or adhesions often touching the pleura, mediastinum and diaphragm; the interlobar fissures may also show some degree of thickening. Restitution to normal in this advanced state is, of course, beyond hope and any likelihood for clinical recovery extremely remote and even totally unexpected. The outlook is worse if tuberculosis should intervene. The superimposed tuberculosis leads to cavitation, further fibrosis and to destruction of those zones of the normal parenchyma tissues wedged in between the silicotic nodular masses and the periphery of the lungs.

On the behavior of pulmonary blood flow in the early stages of silicosis, up to and including the stage of perilymphatic nodulation, we have no data as yet, but in the advanced stages of silicosis with or without extensive tuberculosis our results demonstrate that the pulmonary blood velocity is normal both in the arterial and venous pulmonary circuits. This is particularly interesting in view of the fact that the process from the beginning is diffuse and peripheral and lasts for years.

Since pulmonary blood flow is retarded, practically speaking, only with the advent of congestive failure, these circulatory tests offer a simple practical means of detecting cardiac failure among silicotics

where right ventricular hypertrophy and its terminal lethal failure are not rare. The right heart enlargement and its final picture of congestive failure resemble in all features the similar pictures associated with other chronic pulmonary conditions (*cor pulmonale*). The application of these tests in silicosis discloses that the extensive and profound fibrotic alterations, with diffuse pericapillary and perilymphatic involvement cause no derangement of pulmonary blood flow.

TABLE 2.—SILICOSIS. NORMAL PULMONARY BLOOD VELOCITY IN 10 CASES OF ADVANCED SILICOSIS, 5 OF THESE CASES ALSO HAVING ADVANCED PHTHISIS. (FROM THE SEA VIEW HOSPITAL.)

Name.	No.	Age.	Silicosis.	TB.	Ether time: velocity in pulm. *arterial* circuit. Seconds.	Saccharin time: velocity in entire (crude) pulm. circulation. Seconds.	Difference between II and I: velocity in pulm. *venous* circuit. Seconds.
M. S.	922–28	53.0	+	0	7.5	12.5	5.0
E. D.	11315–35	43.0	+	0	6.0	14.5	8.5
J. H.	10989–34	65.5	+	0	6.0	18.0	12.0
F. C.	6711–32	45 0	+	0	5.5	16.0	10.5
V. S.	9042–33	57.0	+	0	5.5	14.0	9.5
M. S.	11413–35	30.0	+	+	5.0	14.0	9.0
W. G.	10926–34	54.0	+	+	8.0	17.5	9.5
V. S.	11064–34	55 0	+	+	5.0	13.0	8.0
H. K.	11555–35	35.0	+	+	5.0	13.0	8.0
J. S.	11335–35	54.0	+	+	6.0	15.0	9.0

Similarly, peripheral and diffuse (centrifugal) in distribution is the fibrotic process observed in conditions associated with excessive and persistent elevation of the pulmonary blood pressure, as, for example, in chronic mitral stenosis, in advanced emphysema, in a block of the lesser circulation by external pressure. The pathologic change is chiefly in the arteriocapillary bed, although in many cases the alterations include elastic fiber hypertrophy running through the walls of the entire pulmonary vascular tree. These latter changes particularly are the result of pulmonary hypertension and blood velocity plays no part.

The separation of the effects of pressure from those of velocity is readily observed in the larger vascular system. Thus, it is almost commonplace among hypertensives with marked elevation in blood pressure to find no disturbance in the rate of blood flow unless heart failure supervenes. The lesser circulation appears to be no exception to this general rule, and this is illustrated by our results of normal blood flow figures in cases of mitral disease* tested while free of congestive failure and in advanced emphysema* patients also free of congestive failure.

In emphysema the responsibility for pulmonary hypertension has been placed upon the misshaped or enlarged alveoli which are

* These tables have been omitted at this time and will be published in a future communication.

supposed to exert compression upon their adjacent capillaries. This conception, advanced by Cloetta,[12] if valid, confirms our belief based upon our own blood velocity figures and the antecedent results of Weiss and Blumgart,[13] that pulmonary hypertension and the rate of pulmonary blood flow are independent processes.

Summary. 1. The fibrosis in pulmonary disease assumes two main forms: (*a*) A diffuse type involving the vast capillary alveolar bed, associated, as a rule, with pulmonary hypertension and observed in emphysema or in obstruction to the lesser circulation (mitral stenosis, kyphoscoliosis, etc.), and (*b*) a circumscribed or "patchy" fibrosis involving the parenchyma and encountered in tuberculosis, carcinoma, etc. In silicosis the diffuse type is present early and the second, or patchy, form appears much later.

2. From a vascular point of view the heart and lungs are one organ; the lungs represent an enormous vascular sponge of ramified vessels stemming from the heart and surrounded by air sacs through which gases are exchanged between the circulation and the outside atmosphere. With this concept in mind it is not surprising to find that pulmonary disease and conditions associated with marked fibrosis remain extravascular, as a rule, and that when the peripheral vascular lung bed becomes involved a concomitant state of pulmonary hypertension is the rule. The heart, if at all affected, is drawn into the picture secondarily, either (*a*) by developing hypertrophy of the right ventricle as a response to this hypertension, in some cases accompanied by the terminal picture of so-called right heart failure; or else (*b*) the heart responds by altering its volume output as a compensatory reaction to an increase in the $A-V$ difference, this difference following as a result of an interference in gas exchange through a pathologically altered alveolar wall.

3. Unless cardiac failure (congestive failure) intervenes, the rate of pulmonary blood flow remains normal in both arterial and venous circuits in all pulmonary fibrotic conditions. To this there are few exceptions. As in other fibrotic conditions, the rate of pulmonary blood flow in silicosis is not deranged unless heart failure sets in.

4. The rate of pulmonary blood flow is retarded in the venous channels in the presence of cardiac congestive failure.

5. In a few instances of pulmonary fibrotic states the velocity of blood flow was retarded in the pulmonary arterial channels. Here the fault would appear to be in the alveolar membrane.

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MUMPS ORCHITIS.

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The main importance of the occurrence of orchitis in mumps is the possibility of atrophy with subsequent sterility and impotence. Sterility is, of course, lack of sex cells, while impotence[1] refers to the inability to perform the sex act. There are a number of causes for each, but the two are frequently confused. Other symptoms, to be further discussed, complicating the orchitis, may become very serious.

Historically, mumps is an ancient disease. Protalongo[2] was the first to recognize its contagious nature. As in most present-day texts, the disease is considered in a work on Epidemiology and Public Health published in 1922 by Vaughan.[3] Hippocrates was the first to mention testicular involvement, as seen by the following concise description from Vaughan:[4] "Some again, after a while, had painful phlegmons upon the testicles, sometimes upon one, sometimes upon both. Some had fevers, others none; most of them trouble and fatigue enough; but with respect to the chirurgical part they did very well." Hamilton, in 1752, recognized testicular atrophy as a possibility.[5] American army officers reported camp epidemics during the World War.[10, 11] The paper of Wesselhoeft,[12] published in 1920, is the most complete and up-to-date résumé on

mumps orchitis, although other statistics have been added later.[13] Since Hippocrates, orchitis has been recognized by nearly everyone, but especially since the nineteenth century, as a definite and serious complication.

For this study the case records of two Philadelphia hospitals are cited in an attempt to check on certain data found in the literature. Fourteen cases were all that could be found on file at the Hospital of the University of Pennsylvania;[14] 269 cases had been admitted to the Philadelphia Hospital for Contagious Diseases from 1918 through 1933.[15]

Though contagious, mumps is a relatively mild infection. The age incidence varies greatly; some writers[16] limit the disease to childhood while others[16, 17] note its occurrence in both children and adolescents. In the cases at the Philadelphia Municipal Hospital[15] there were two definite and distinct peaks: one in childhood, and the other in adolescence (Fig. 1). There has been a seasonal variation in incidence—according to some,[18] more cases are seen in the winter and spring, while other sources place the peak from November through February.[13] The sexes are equally susceptible[3, 18] and the actual figures in the Municipal Hospital cases were males 144 and females 125. Negroes seem more susceptible to mumps than whites, as shown by army statistics, where the morbidity was three times as great in the colored troops. The reverse was true in the Municipal Hospital cases—7 to 1 in favor of the whites. The higher proportion of cases in colored patients coming from the rural districts where there are more susceptibles and fewer immunes argues for the presence of a definite immunity from one attack, according to some writers. This immunity is generally undisputed,[3, 10, 13, 19, 20, 21] though some[10] consider it very fleeting. The injection experiments of Hess[22] and Gradwohl *et al.*[23] give further evidence of immunity production. Second attacks are mentioned in the literature[11, 24] and were recorded in both the hospitals series used for this paper.[14, 15] The degree of exposure and the acquired immunity are the determining factors in group and community incidence.[18, 86] To these must be added as further factors: general health, crowding, and the occurrence of carriers.[13] Contact is held indispensable to spread.

Transmission experiments[21, 25] have indicated that mumps is a virus disease; Rivers[26] says, "the evidence, however, that mumps is caused by a virus is suggestive enough to warrant its inclusion in a discussion of virus disorders." Other theories of causation include: salivary retention,[27] rheumatismal factors,[28] a micrococcus,[29, 30, 31] a diplococcus,[32, 33] a diplobacillus,[34] and recently a specific spirochete[35] in association with a small Gram-negative bacillus.[30] The portal of entry of the virus is obscure, although it is probably the upper respiratory tract.

Most writers agree on an incubation period of about 18 days. The mode of onset varies greatly, though malaise, slight fever, and tenderness at the angles of the jaw is the commonest sequence of events. Later, there is usually swelling of the parotids, a sensation of heat, limitation in the opening of the jaw, with headache and

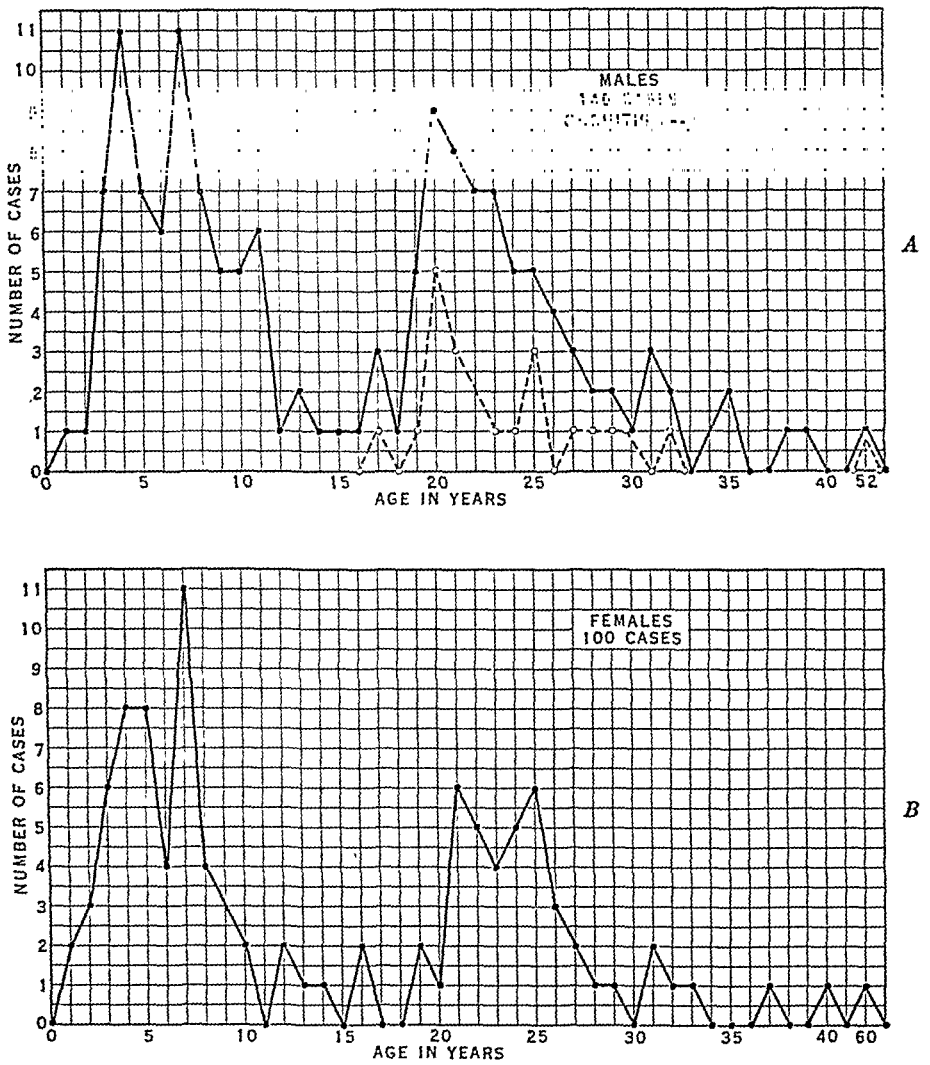


FIG. 1.—Age incidence of mumps and its orchitis: 246 cases—Philadelphia Hospital for Contagious Diseases.

earache. There is always a leukocytosis, principally neutrophils. Other findings compatible with a febrile state result, but the fever is often very slight. There may be gastro-intestinal symptoms. Rivers says, "During the course of mumps in an occasional patient, symptoms and signs referable to the central nervous system develop."

Involvement of the seventh and eighth nerves has been noted.[36, 37, 38] This is rare in uncomplicated cases. Suppuration never occurs in true mumps. The salivary glands and cervical lymph nodes may be affected.

The description of Hippocrates[32] gives a good picture of the malady: "Swellings appear near the ears, in many cases on one side, in most on both, without a fever or any confinement, but in some with a little fever. In all, they disappear without either inconvenience or suppuration, contrary to the custom of such tumors from other causes. At this particular time, they were naturally soft, large, diffused, without inflammation or pain, and went off universally without any visible signs. Children, young persons, adults, especially those who frequented the public places of exercise, were most subject to them. A few women were also affected. The greatest part had dry coughs, which were soon succeeded by hoarseness."

Etiology and Pathogenesis. The etiologic agent responsible for the testicular affection is the same as that of mumps.[8, 39] Just how orchitis occurs has never been adequately settled, though a number of theories have been advanced.

Before enumerating these, the quite definite relation between the parotids and genitalia should be briefly considered. Paget[40] mentions that occasionally affections of the breasts and labia after mumps in women point to some special connection between the salivary glands and the genital organs. He also mentions the enlargement of the salivary glands of the camel during the breeding season, and quotes Darwin[41] as to the thyroid and odoriferous glandular enlargement in various animals during this same season. Paget further suggests that the salivary glands may in some way have secondary sex characters, in the same category as the hair and voice. Cribb[42] cites 4 cases "which show the connection between the parotids and the prostate, vagina, and ovaries." Tayler[17] suggests a relation between the glands and the testes as an explanation of orchitis. He also cites numerous cases in which, following operations such as hysterectomy, ovariotomy, gastrostomy, circumcision, or in other cases such as lithotomy, typhus fever or penetrating abdominal wounds, a secondary parotitis developed, indicating a genito-parotid interrelationship. Wesselhoeft gives many citations from Owen,[43] Darwin and others to prove this relationship, among which are: (*a*) Musky odor from crocodiles' submaxillary gland at the breeding season; (*b*) enlargement of elephants' face glands at the rutting season (also applicable to the Indian antelope); (*c*) acute simple parotitis resulting from genital injury by such maneuvers as catheterization, prostatectomy, pessary insertion, pelvic operations, deliveries and abortions; (*d*) parotid swelling occurring with menstruation, replacing menstruation, with pregnancy, during and after the menopause; (*e*) postoperative parotitis as in Paget's cases.

A. Most authors regard orchitis as a true metastasis, or blood stream infection, localizing in the testis. Edwards[14] takes this view because of the rarity of primary orchitis. Walker[15] believes that, while the parotid is always involved in mumps, in certain cases the genital affection is so marked that the parotids remain unnoticed. Fougerousse[16] finds that the use of diathermy on the parotids is of value in the prevention of orchitis and thinks that this is good evidence for the metastatic mode of spread. Trousseau[19] says orchitis is a metastasis and that its occurrence proves the existence of a sympathy between the parotid gland and the genital organs. Wesselhoeft considers the extensive glandular involvement throughout the body an objection to any theory but the septic. He lists the glands and organs which may become involved: ovary, Bartholin's glands, mammary glands in males and females, lymph nodes, lachrymal sac, pancreas, thyroid, thymus, epididymus, prostate, bladder, urethra and genitalia. A case cited by Gould[47] and diagnosed "atypical mumps" was characterized by the involvement of one entire side of the body. Others[11, 48, 49] definitely state that the orchitis of mumps is not a blood stream metastasis.

B. Another theory that has been advanced is that infective matter is transferred from the mouth to the penis by the fingers, whence the urethra and subsequently the genitalia become involved.[12, 46, 50] This has been easily disproved by prophylactic experiments in which the hands were kept clean and the genitals surrounded by linen bags.[51] The incidence of orchitis was unaltered.

C. A third theory is that of glandular affinity and localization. This might operate by some means explainable by Rosenow's special affinity theory and that of Abderhalden as regards the chemotaxis of tissue cells to poisons and foreign substances. That the genital glands are merely one of the sites in the body affected by mumps is the theory held by Currier,[52] Comby,[6, 7] Gerard,[49] and Tayler.[17] I averan says that orchitis is merely a symptom of mumps in the same way as is parotitis.

D. Testicular trauma may predispose to orchitis[11, 12, 53] and it is also said that absolute rest in bed may help to prevent the onset of orchitic complications.[54] However, in two epidemics at Rugby in England, putting the cases to bed had no influence on the incidence of testicular involvement.[48] Moreover, cases of orchitis have been observed under circumstances where no possible trauma could have been sustained. Chill and exposure are probably not important factors in the onset of orchitis.[55] All these factors may, however, play contributory rôles.

Incidence of Orchitis. There is some confusion about this interesting and important subject, due to the fact that compilations of data by different authors not seldom overlap; and again, the figures quoted by different writers from apparently the same sources are at variance. Representative statistics are listed in the following

tabulation (Table 1). The average of the percentage incidence in those series comprising 1000 or more cases is 18.2%.

TABLE 1.—INCIDENCE OF ORCHITIS IN MUMPS.

Author.	Incidence in per cent of cases seen.	Cases.	Reference No.
Catrin	18.5	10,601	56
Wesselhoeft	18.0	8,000	12
Benard	15.0	5,000	57
Radin*	13.9	4,397	10
Benard	20.0	2,000	57
Longuet	25.0	1,555	58
Brooks	24.0	1,059	11
Comby	30.1	699	7
Capitan*	18.4	690	59
Granier*	23.2	495	27
Benard	22.0	408	57
Rilliet and Barthez	43.5	230	60
Philadelphia Hospital for Contagious Diseases	17.1	144	15
Thierry de Maugras	29.0	76	63
Chatin	24.3	37	64
Vidal	38.4	26	61
Busard	50.0	26	62
Hospital of Univ. of Pennsylvania	28.5	14	14
Laveran†	33.0	...	8
Hudelo†	60.0	...	65
Bieberbach and Vibber	18.0	...	66
Fougerousse	20.0	...	46
Macleod	20.0	..	67
Tillim	26.3	...	16
Tillim	75.0	...	16
Saucerotte	100.0	...	68
Chateauroux	100.0	...	69
Vedrennes	26.0	...	72

* Included in series of Wesselhoeft, reference 12.
† Quoted by Benard, reference 57.

It is interesting to note the age at which orchitis may develop. Acker[71] says that orchitis is rare in children. He quotes the observations of Rilliet and Barthez (taken from Holt[72]), which note that orchitis was seen in only 10 of 230 cases of mumps, 3 of these 10 under 15, and none under 12 years of age. Laveran[8] did not see orchitis in any boy under 14 in a large epidemic, and states that most of the cases were in the age group of 23 to 38. Lowe[73] observed most of his cases between 17 and 40. Stevens[74] regards this complication as uncommon before puberty. Béclère,[75] Dukes,[48] Sinclair[18] and a recent editorial writer[76] all say that mumps orchitis practically never occurs before puberty, and Vaughan[3] says that it never occurs before the 15th year. Wesselhoeft[12] observes that orchitis is usually confined to puberty and adolescence, but notes that there have been three exceptions: 1 in a 9 months' infant, 1 each in boys of 9 and 11 years of age. He also says that the incidence of orchitis decreases in direct proportion to the decrease of mumps in advancing years. Comby[7] cites cases of orchitis in boys aged 14, 12, 13, 9, 4

and between 15 and 17. In our series of the Philadelphia Municipal Hospital,[15] most of the cases were between 18 and 30, the oldest 52 and the youngest 17 (Fig. 1, A); all the cases at the Hospital of the University of Pennsylvania[14] were in the early twenties.

In a series of 694 cases, Macleod[67] observed that orchitis occurred in the second attacks of mumps in 17, and in the third in 1. Brooks[11] says that where there has been orchitis, the testes are sure to become involved again. Mitchell[77] has reported a case of mumps orchitis in an undescended testicle in a 33-year-old negro. Another such case in a boy of 14 was reported by Ross.[78]

The incidence of orchitis, then varies greatly with the author, the number of cases in each series, and the type of epidemic or environment. While the fluctuation is great, the majority of the larger series shows an incidence of about 18.2%; only 5 cases of orchitis have been reported prior to the 12th year; and occurrence of orchitis is generally limited to the time of puberty (the 14th to 15th year) or later.

Symptoms and Signs. The symptoms and signs which may be noted in a case of orchitis are varied and numerous, depending on a number of factors. The mode of onset, the severity of the affection, and the degree of involvement (unilateral or bilateral) are paramount.

TABLE 2.—DAY OF APPEARANCE OF MUMPS ORCHITIS.

Author.	Usually.	As early or as late as:	Reference No.
Macleod	7th	44th	67
Mitchell	7th		77
Dukes	7th or 8th		48
Catrin	4th to 8th		56
Servier	3d to 6th	1st and 10th	24
Béclère	2d		75
Wesselhoeft	Before subsidence of parotitis		12

With regard to the mode of onset, most authors state that mumps orchitis is generally a sequel to mumps parotitis,[55] and this was the invariable finding in the two hospital series studied for this paper. The time of onset varies greatly (Table 2). It is stated[75, 56, 44] that exceptionally the orchitis may precede the parotitis (as far ahead as 13 days[79] or only 3 days[80]). Wesselhoeft[12] enumerates 30 cases and Comby cites cases of Saucerotte[68] in addition. The French literature contains numerous examples[56, 8, 74, 75, 81, 82, 45, 49, 83] of orchitis without any parotitis whatever. Some of these cases are listed by Wesselhoeft (64 cases) and Comby[6] has added others (84) among which are epidemics at Geneva and Danzig. Some of these cases have been termed "spontaneous" or "abortive" orchitis.[70, 56, 85, 87–90] Whether or not all of these are mumps is open to question.

The severity of the affection depends on the degree of involvement. When both testes are involved, the condition is certainly much more severe. Unilateral orchitis is commoner than bilateral, and it is said that the bilateral variety is very rare.[91, 74, 90] In a tabulation of 1200 cases[12] it would appear that the unilateral is two or three times as frequent. Other figures are given in Table 3. There

TABLE 3.—FREQUENCY OF BILATERAL ORCHITIS IN MUMPS.

Author.	Bilaterality, per cent of cases seen.	Reference No.
Madamet	0	92 (7 cases)
Macleod	16	67
Radin	20	10
Laveran	28	8
Smith, G. C.	30	93
Catrin	30	56
Wesselhoeft	25 to 35	12 (1200 cases)

is little difference between the frequency of involvement of the right and left sides.[8, 67] If the affection becomes bilateral, the second testicle is involved some time after the first, usually about the second day, and goes through the same cycle as did that first hit. Various attempts have been made to associate the side of the testicular involvement with that of the preceding parotitis, and to obtain some data from the severity of the parotitis in order to prognosticate as to possible orchitis and its severity. In general, there is no relation.[93] It has been stated[90] that orchitis is to be feared if there is considerable parotid swelling, submaxillary gland induration, and pronounced lassitude, but the sequence of events is not at all constant. Brown[55] reported 9 cases of orchitis where the involvement of the genitalia was ipsilateral with the parotitis in 8, and bilateral in the 9th. Acker[71] says orchitis is usually on the left side and on the same side as the "mumps." Many others disagree, saying what is generally accepted: that there is no relation whatever.

In general, the temperature is one's best guide, both in diagnosis of genital involvement at an early stage and in following its subsequent course. In the usual case, swelling and tenderness in the parotid gland on one or both sides has occurred and is practically subsided. The temperature starts to rise, and at the same time a certain malaise and anxiety is noted. Soon the patient begins to complain of tenderness in the body of the testicle on one side. Rapid swelling commences as the fever rises, and fluctuation may be noted.[67] (Edema usually appears on the 4th day, or often when the testicle is either enlarged or just starting to get smaller, but it is not always seen.) The slight tenderness increases in severity and soon gives way to very real pain, caused apparently by stretching of the tunica albuginea, the tunica vaginalis testis, and the scrotum. At the height of the involvement, usually on the 3d or 4th day, the

testicle may be enormously enlarged and the pain so severe that large doses of morphin will not relieve it. With the rise in temperature, which may reach 105° F., goes a parallel rise in pulse rate, while the respiratory rate may or may not be increased. Anorexia, thirst, weakness, headache, vomiting, "white tongue," and an "idle mind" are also observed.[90] The testicle becomes very hard and tense, and this condition may persist 4 to 6 days. Gradually the swelling subsides, and the fever drops. The recovery is slower than the involvement, and some fever may persist until all swelling is gone. Some authors describe a true crisis, at which time all the symptoms are exaggerated, and after which recovery is extremely rapid.[55] This probably occurs only in the most severe affections, and certainly the slow subsidence, or lysis, is more usually seen. The usual course of orchitis is about 10 days.[74] The testicle during the lysis becomes smaller, usually firm, but shows pitting pressure if there has been scrotal edema. Some authors say that the epididymus is the first genital structure to become involved, and that it is always implicated.[10, 54, 56, 90, 94] Others note epididymitis at a later stage only[19, 11, 24, 95] or not at all.[96] This is important from the prognostic point of view, since a temporary sterility may clear up if the trouble is only epididymal. The point is too controversial to be settled at the present time. It is generally said that primary epididymal involvement is seen in tuberculosis, gonorrhea, influenza and infectious diseases, but that genital affection in gout,[97] typhoid fever,[98, 97] undulant fever[70] and syphilis is orchitic. The spermatic cord and vas may or may not be involved.

Other rarer symptoms are noted from time to time. Oliguria, backache, nausea and vomiting may occur early in serious cases. On the other hand, polyuria, urethral discharges, chills and excessive perspiration have also been described, while some[44] say that urethral discharge, bladder irritation, suppuration and permanent changes in the epididymus are always absent. Rigidity and pain in the abdomen, especially in the inguinal areas along the course of the cord (*i. e.*, a deferentitis or funiculitis) have been cited by several writers as signs whereby appendicitis or other acute abdominal conditions have been confused with the true situation. In the very seriously affected, especially when the temperature stays as high as 104° to 105° F. for 24 to 36 hours, central nervous system symptoms such as delirium, stupor, and maniacal outbursts may supervene.[54, 94] In these cases, meningitis,[99] or encephalomyelitis[110] is sometimes suspected and may often be present (possibly the aseptic type), and the patient must be kept under severe restraint. There are many such cases recorded and the author knows of at least 3 other unreported occurrences.

A number of studies of the blood has been made on patients with orchitis. Investigators disagree on the findings. Feiling[54] states

that orchitis often does not affect the blood picture, and that while leukocytosis may be present in orchitis, there is also seen in many uncomplicated cases a rise in the white cell count of the order of 6000 to 13,500 with relative mononuclear increases. Wile[100] finds a constant lymphocytosis and a slight rise in the neutrophils at the onset of the orchitis. Bieberbach and Vibber[66] note a leukocytosis of 14,000 with 36% lymphocytes. In the 4 orchitis cases at the Hospital of the University of Pennsylvania, the white cell counts were 16,000, 9600, 18,600 and 12,800, while those in the uncomplicated cases varied from 4400 to 9800.

The failure to recover completely from orchitis is noticed subjectively in diminution in sexual power, or objectively in atrophy of one or both testes. It is generally said that "atrophy" of the testis occurs quite regularly.[13, 54, 7, 78, 74] This term is not at all clear, as it is frequently very loosely used. Most writers seem to mean only a reduction in size of the testis. With reduction of the enormous swelling and the cessation of pain the testes become soft and are then decreased in size by progressive stages. Later the testis may seem entirely normal or smaller than normal; and while the amount of reduction varies greatly[90] it may be only temporary, with a rapid return to its pre-orchitic size. Therefore, while an examination made immediately after recovery from orchitis may reveal a small testis, later examination would perhaps show one of normal size or of half the normal size.[57, 56] Statistics on "atrophy" following mumps orchitis are given by many authors,[6, 8] and its incidence is generally put at between 40 and 60% by most,[24, 27, 92, 101, 66, 56, 49] though higher (63%) by others.[8] However it may be that "atrophy" is only an anatomic occurrence (Bénard[57] states that he has seen but 2 cases of real atrophy, both unilateral), the fact remains that cases of physiologic atrophy are recognized. Bilateral "atrophy" is, of course, much rarer than the unilateral, and Granier[27] says few have been seen. Stevens[74] states that even bilateral atrophy does not mean loss of procreative powers. The cause of atrophy is essentially a pressure necrosis, and the results are aspermia and the loss of certain reflexes such as the cremasteric.[56] Wesselhoeft[12] describes areas of healthy tissue with normal functioning tubules separated by fibrosed areas of necrosis. There are usually no symptoms from an atrophied organ, but neuralgic pain may be manifest. The greater the severity of the orchitis, the better the chance of atrophy, and the more complete its degree. There are definite psychologic effects associated with testicular atrophy,[78, 102] but at the same time, it has been said[78] that an atrophied organ is better than none at all (*e. g.*, after removal by surgery). Orchitis does not always mean subsequent necrosis.

While the possibility of sterility following "atrophy" from mumps orchitis is mentioned by nearly all authors, yet only 2 cases of physio-

logically proven sterility are recorded.[102, 103] Wesselhoeft reports a sterile marriage after mumps orchitis; this, of course, proves nothing. He notes that cases of feminism have occurred, particularly that mentioned by Comby.[104] The latter says that effeminacy with enlarged breasts and eunuchoid voice can occur. Milder results than complete sterility, such as decreased sexual appetite or lessened ability to perform coitus (*i. e.*, impotence) are observed.[8] It is said,[12] however, that sterility results more often from atrophy of the prostate than that of the testis, and that the prostatic involvement should receive more attention. It is also a fact that bilateral orchidectomy causes prostatic atrophy. Therefore perhaps the prostatic involvement in mumps is secondary to the primary testicular lesion. Huber[105] remarks upon complete frigidity in a case, apparently a second orchitic attack. At the other extreme, Bénard[57] maintains that sterility from atrophy after mumps orchitis is practically unknown, stating that there was only 1 case in 175,000 cases of mumps in the French army, and he gives a number of statistics on these cases which might justify his stand. His chief arguments are: *a*, that the chances for bilateral orchitis after mumps are only 1½ to 2 in 100; *b*, that even partial bilateral atrophy is very rare; *c*, that after a suitable period of time many testes supposedly hopelessly atrophied were not so crippled and, *d*, that there are only 2 cases of functionally proved atrophy in all literature. Laveran[8] also belittles the possibility of sterility, quoting Velpeau[106] to the effect that "mumps is the least grave of all orchitis causes." On the other hand, many cases of sterility undoubtedly result, even though few[111, 112] appear in the literature. To support this statement, the author knows of 2 cases, communicated to him personally, which have resulted in total sterility, unquestionably due to the mumps orchitis which both patients contracted.

In addition to the case of feminism cited by Lereboullet,[102] another has been reported by Laignel-Levastine and Courbon:[103] A young soldier, aged 22, tall, wiry, strong in every respect, and especially active sexually, contracted mumps which was complicated by double orchitis. He was hospitalized for 26 days, during which time his fever went over 40° C., he had neck pains and Kernig's sign, as well as a meningeal reaction (the spinal fluid showed increased albumin and 3 lymphocytes per cmm.). Seven months later his testicles were atrophying, his breasts were enlarging to the point of being clearly visible. Power of erection, sexual desire and vigor were all decreased, so that he felt a peculiar weakness after attempts at coitus. He grew weak after all forms of muscular exercise and his secondary sex characteristics changed to those of a woman. His legs were large, his abdomen big, his breasts quite enlarged, and his penis and testicles atrophied. There is apparently

no report on the subsequent progress of this case. It is most unusual, and it may well be that there was some endocrine factor in addition to the mumps.

Pathologic Anatomy. The pathologic changes occurring in the testicle during an attack of orchitis are almost entirely unknown, since surgical operations are but rarely performed, and as patients nearly always recover they do not come to autopsy.

A few cases have been operated upon. Smith[93] reported 2 in which operation was performed in the hope of preventing atrophy. In both of these there was considerable enlargement of the hard, smooth testicle. On incision of the tunica vaginalis, an ounce of yellowish turbid fluid, free of bacteria and parasites, was obtained. The testis appeared bluish, firm and elastic, and showed punctate hemorrhages. The epididymus was enlarged, soft, and red to black in color. The cord was edematous. In a microscopic study of 1 of these cases, a non-uniform involvement was specially noted. The tubules were distended with an exudate made up largely of neutrophils and endothelial phagocytes. Destroyed tubules, hyalin degeneration, and lack of mature spermatozoa were also observed. Between these destroyed tubules fairly normal tissue was seen, as well as a few sex cells in mitosis. The intertubular connective tissue was edematous and contained an exudate made up of fibrin, red and white blood cells. The impression was that the involvement had proceeded along the intertubular connective tissue or had progressed by way of the tunica albuginea. The latter was edematous and showed hemorrhages and exudation about the bloodvessels, but no necrosis.

Comby[6] cites the observations of Réclus[107] on a removed testicle. The gland was soft, flaccid and atrophied. The tunica albuginea was too large for its contained organ, and wrinkled. The substance of the testis was bloodless, opaline and milky white. The cut surface was smooth, showing tubules faintly marked, soft and easily broken. He regarded the underlying lesion as a parenchymatous sclerosis. Malassez[108] made histologic examinations of this organ, and reported the tubules diminished in volume, their epithelium gone, and their form similar to cords. He noted also healthy bloodvessels, and intercanalicular connective tissue that was not thickened. It is reported[12] that a serous exudate appears in the septa and lobules of orchitic testes and the tunica vaginalis is also involved. The scrotal skin becomes red and swollen, and the vas congested. In cats inoculated intratesticularly, epithelial degeneration and interference with spermatogenesis are found.[12] The inflammation seen in orchitis disposes to cancer according to some[78] and sarcoma has been recorded as a later development in such a testis. All other descriptions of the testicle in mumps orchitis are of its external appearance, essen-

tially the same as previously cited. There are some variations. Comby[6] notes that suppuration may occur late in orchitis, and that this may go on to a fatal peritonitis. He also recognizes a chronic orchitis. Ballenger and Elder[101] say that testicular destruction is probably due to some local toxic product of the organism causing mumps, or else it is a pressure necrosis only. If it is due to pressure, it is because the inflammatory swelling is prevented by the inelastic tunica albuginea.

Diagnosis. Little need be said on this topic, except that while orchitis is an easy diagnosis in the midst of an epidemic, it may become very difficult at other times. The history of contact must be carefully sought, and other causes of orchitis must be eliminated. It is said[6] that perhaps the involvement of the epididymus may distinguish the orchitis of mumps from that of gonorrhea.

There are a number of types of orchitis other than that occurring in mumps, in the same way as there are other forms of parotitis, Ballenger and Elder[101] list traumatism, gonorrheal infection, malaria, typhoid fever, scarlet fever, influenza, rheumatism, gout, and they also note that suppuration and atrophy are rare in these cases. To this list, Hughes[96] adds measles, also mentioning that mumps orchitis is by far the most frequent acute inflammatory swelling of the testicle. He notes that suppurative inflammation of the testicle can occur after infection of the bladder or urethra with Bacterium coli, especially in old men with prostatic obstruction. Bieberbach and Vibber[66] add paratyphoid fever, smallpox, tonsillitis and diphtheria to the long list. Various other types of orchitis are mentioned, mainly in connection with mumps, by French writers. Types such as the "abortive" variety, and the "spontaneous" forms, terms which are concerned with the time relation between parotitis and orchitis, come into this category.[6] A type of testicular involvement which Catrin[56] says must be distinguished from the orchitis of mumps because of its mild character is "fluxion testiculaire." A case has occurred in the Hospital of the University of Pennsylvania where a tuberculous origin was suspected.

Treatment. Treatment of orchitis is of two sorts: prophylactic and palliative. The first prophylactic measure to be thought of is the prevention of the disease. This may be accomplished by a quarantine of 21 days, as practised in certain localities for the prevention of contact spread.[13] Some regulations require isolation in separate cubicles. All these measures have been tried, in order to lessen the extremely rapid spread of mumps as observed in camps during the World War. The application of diathermy to the parotids has been mentioned under pathogenesis.[46] In the past several years convalescent mumps serum and, more lately, lyophile serum have been tried extensively[113-119] with very fair prophylactic success. In the prevention of complications in established mumps,

Sailer[51] and Wesselhoeft[12] say that all such measures as boiling utensils, cleaning the hands and preventing infection from reaching the urethra are useless. The faradic current has been used. Others[12, 67, 56] advise absolute rest for a long period after the onset of mumps as a measure to prevent complications, but it is also said[13, 66, 48] that the amount of bodily activity has no effect on orchitis. Some effects have apparently been noted from the use of convalescent serum as advocated by Gradwohl *et al.*[23] Ice packs, testicular elevation and dietary measures may be possible aids.[66]

Most authors say that one should make no attempt to manage the developed case of orchitis, since it must run its course in any event.[54, 8, 90]

There have been many measures suggested in the medical management, as is usually the case when no definite régime is recognized. The most important methods in use include rest in bed with elevation of the testicle and the use of the suspensory bandage. Heat, in the form of a hot-water bottle or poultice, especially combined with an emollient or belladonna ointment, or cold by means of an ice pack is very helpful. Manipulations should not be used in those cases where there is great pain. Other remedies more frequently used are listed for the sake of completeness: ammonium chlorid, tobacco poultices, phenacetin, salol, digitalis;[44] urotropin:[9] aconite, veratrum viride, pulsatilla, biniodid;[73] purges, bland diet;[67, 77] bromids, ichthyol, guaiacol;[13] and quinin mixture.[77] More lately convalescent serum has been tried and some success obtained. Its endorsers[23] say: "We were particularly struck by the remarkable effect of these injections upon the complication of mumps, to wit, a lessening of pain, and in earlier subsidence of swelling, together with an earlier drop in temperature." They saw relief of extreme pain from orchitis in 5 hours. In a recent case of bilateral orchitis,[120] marked improvement was obtained 36 hours after serotherapy. There is no good routine for the medical treatment of orchitis; it is merely symptomatic.

Some cases have been treated by surgery. Abraham[53] advised incision of the testis to relieve tension and prevent sterility. Ballenger and Elder[101] recommend anterior incision through the tunica albuginea in several places to allow bulging, followed by replacement of the organ and closure of the wound. Cases in this series that had been operated upon, and those done by Bieberbach and Vibber,[66] showed good results. Smith's 2 cases[93] were treated surgically for the same reasons and in much the same way. H. Smith[109] reports a case with marked relief after operation. Wesselhoeft says incision and relief of pressure may help very materially.

Recently advocated treatment by hypodermic use of antuitrin-S may alleviate sterility produced by mumps, though not enough cases have as yet been observed.[111, 112]

Summary and Conclusions. 1. Mumps is caused by a virus.

2. Orchitis in mumps is important because of the possibility of subsequent sterility or impotence.

3. There is a definite relation between the parotid gland and the genitals.

4. Orchitis usually follows parotitis and is more often unilateral than bilateral.

5. Orchitis is probably a hematogenous metastasis.

6. Orchitis is most frequent at the age of puberty; its incidence in a large number of cases is about 18.2%.

7. Rise in temperature; swelling, tenderness, pain in the testicle; subsidence of fever by lysis; later variability in size of the gland are prominent symptoms of orchitis.

8. Orchitis may be complicated by a number of conditions, among which may be included: *a*, Meningitis, and other central nervous system involvements; *b*, "atrophy" of the testis occurs in 40 to 60%; *c*, impotence and sterility certainly do occur.

9. The lesion in orchitis is probably a parenchymatous sclerosis.

10. Diagnosis in epidemics is easy; it may be difficult in the absence of an epidemic or of marked parotitis.

11. Prophylaxis is by prevention of the disease; treatment is purely symptomatic.

12. The use of convalescent serum or surgical incision may give good results.

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A ROUTINE DIAGNOSTIC PROCEDURE FOR THE PATIENT WHO ENTERS THE HOSPITAL IN COMA.

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Supplementing previous articles,[1,2] on the causes and differential diagnosis of coma in patients entering a general hospital, the present study aims to point out the need for a routine diagnostic procedure and to offer, from the experience gathered in this study, such a coma routine.

Of the 1167 patients (3% of the total hospital admissions) who entered this hospital in coma, in 1933, 1101 (94%) were diagnosed correctly on admission. It should be pointed out that 690 of these patients were in alcoholic coma, and 688 of these were correctly diagnosed on admission. Of the 477 non-alcoholic patients, 64 (13%) were incorrectly diagnosed on admission. Though these figures seem unusually good when compared to Bissell and Lecount's[3] statistics, the two studies are not comparable inasmuch as they analyzed only cases coming to autopsy, and the excluded recovered cases were probably easier to diagnose. In the total group of 66 cases which were incorrectly diagnosed on entry in our series, 47 resulted in death. We estimate that in 18 of these, death would possibly have been preventable if a correct diagnosis had been made on admission and appropriate treatment started at once. We further feel that the lack of a proper coma routine may have contributed seriously to the failure to make the correct diagnosis in these cases.

The medical student ordinarily receives very little instruction from the school and textbook in the practical matter of handling the patient in coma from unknown cause. The hospital intern soon acquires skill in this direction by experience. But the intern staff, which in the general hospital is the group responsible for the rapid and efficient analysis of these patients, is constantly changing. To insure uniform efficacy, it is suggested that a fairly rigid procedure be set up and followed by the house physicians as a coma routine.

From a consideration of the records of the 1167 patients previously referred to, the following data in relation to a coma routine have been accumulated.

The Importance of the History. Among the patients who entered the hospital in coma of non-alcoholic origin, the history was of immediate diagnostic importance in over 80% of the cases. Especially significant in the history were: the type of onset, injury; ingestion of poisons, infections, convulsions, headache and previous illness (diabetes, kidney trouble, heart trouble, high blood pressure). We estimate that among the cases incorrectly diagnosed, the lack of an adequate history was largely responsible in approximately 45% of the cases.

In view of the paramount, and, we may say, largely unappreciated, importance of the history in these cases, the authors feel that in coma cases every effort should be made to bring forth the history as soon as possible. The first representative of the hospital to see the patient, usually the ambulance man, should be instructed to bring to the hospital with the patient any relatives or friends who may help furnish the history of the case. If this is impossible, he should make every effort to obtain the essential points in the history while the patient is being made ready to leave for the hospital. A short delay at this time is far preferable in most cases to bringing the patient in without a history. If the ambulance man is unable to obtain a story, he should leave word with some responsible party that it may be "a life or death" matter to find out the patient's history and bring it to the hospital as soon as possible.

In spite of these precautions, patients will still be brought to the hospital without a history. The physician in charge should make it his first duty to have the police notified that the history in the particular case is a vital matter. The Boston police have been most coöperative in obtaining such histories for the hospital in a rapid and efficient manner. In some communities it may be that this function would be more suitably assigned to the social service department.

The Importance of the Physical Examination. It may seem unnecessary to stress the importance of a complete and thorough physical examination on every patient who is first seen in coma. But mistakes in diagnosis are not infrequently made because of an inadequate examination on patients considered alcoholic. The telltale odor of alcohol on the breath does not mean necessarily that the coma is due to alcoholism. In the group of incorrectly diagnosed cases referred to above, 5 patients were thought to be in coma because of alcoholism, whereas it developed later that 3 had severe brain injury with fractured skull, 1 had a subdural hematoma and 1 had lobar pneumonia.

The failure to examine the eyegrounds in 1 of the cases in this series resulted in an incorrect diagnosis in a patient with brain tumor. In 2 cases, the diagnosis of subarachnoid hemorrhage in 1 and meningitis in the other was missed because the examiner in each case failed to test for a stiff neck. Other points in the physical

examination which have been of particular diagnostic value in this series of coma cases are listed below in the summary.

From the practical standpoint, it cannot be overstressed that patients who enter the hospital in coma should be treated as emergency cases. The intern to be directly in charge of the patient should be called at once to examine the patient, preferably while the patient is still in the admitting room. Special diagnostic measures, if necessary, can then be undertaken without delay, and therapy started as soon as possible.

The Importance of Roentgen Rays. In some cases, Roentgen rays are of definite diagnostic value in determining the cause of coma. In the series of cases analyzed by the authors, they were of assistance in establishing the diagnosis in 74, or 6% of the total cases. Among the cases incorrectly diagnosed, they would have been of service in making the correct diagnosis in 15 cases, or 23% of the total cases incorrectly diagnosed.

The chief value of the Roentgen ray in these cases is as an aid in establishing the diagnosis of coma due to brain injury, through the demonstration of fractured skull. Roentgen rays of the chest are of diagnostic value in patients with coma due to pneumonia, or cardiac decompensation.

Because of the relative frequency with which fractures of the skull are overlooked in patients who enter the hospital in coma, Roentgen rays of the skull should be taken routinely on comatose patients who show evidence of injury. Unless the patient is in shock, they should be taken before the patient is sent to the wards from the admitting room, thus eliminating delay and unnecessary moving of the patient.

The Importance of Laboratory Work. It is well recognized that laboratory data can be of great assistance in making the diagnosis in cases of coma of unknown cause. In fact there is a tendency in coma cases to pay too much attention to laboratory studies and not enough to a careful history and examination of the patient. It is noteworthy, that in not a single case of those incorrectly diagnosed in this series, was the lack of sufficient laboratory data to blame. In our total series, laboratory work other than the lumbar puncture was of diagnostic value in 107 cases (9%).

The various laboratory procedures, and the relative order in which they should usually be done, are indicated below in the summary.

The Importance of the Lumbar Puncture. In some communities the lumbar puncture is still looked upon askance as a dangerous procedure, to be undertaken only on rare occasions by the neurologist or neurosurgeon. But the safety and value of the lumbar puncture in the hands of the general practitioner have been well established. In cases of coma of unknown origin we regard it, after the physical

examination and history, as the most important diagnostic procedure. In 174 cases, or 15% of the total cases in this series, the lumbar puncture was of critical diagnostic significance. Among the cases incorrectly diagnosed, 16 (24%) would probably have been diagnosed correctly had a lumbar puncture been done.

The lumbar puncture should be made a routine diagnostic procedure in cases of coma in which there is evidence of injury (except in the presence of shock), in cases with neurologic signs or symptoms, and in all cases where the diagnosis is obscure. The various observations and tests to be done on the cerebrospinal fluid are noted below.

Summary. The essential practical points in the above discussion have been abstracted and grouped in the form of a chart suitable for display in the hospital admitting room and intern laboratories (see chart). From the evidence presented, it is felt that the coma routine herein described will be of value in the proper handling of the patient who enters the hospital in coma.

Coma Routine. Patients entering the hospital in coma are *emergencies.* A life may depend on the rapidity with which a *diagnosis* is made and *treatment* instituted.

I. HISTORY. This is of paramount importance. If no friends accompany the patient, talk to the *ambulance man.* Then send out the *police* or a *social worker.* Inquire especially about: *type of onset, injury, alcohol, other poisons, infections, convulsions, headache, previous illness* (diabetes, kidney trouble, heart trouble, high blood pressure).

II. PHYSICAL EXAMINATION. Be rapid and thorough. Remember this is essentially veterinary medicine. Your patient cannot help you. Use your *eyes:* Note the patient's color, posture, movements; look for *wounds,* especially in the scalp. Examine the *pupils,* the *eyegrounds,* the *eardrums,* the *throat.* Use your *Nose:* Is there an odor to the *breath*—alcohol, acetone, illuminating gas? Use your *hands:* Feel for a *stiff neck,* for *fractures,* for *muscle* and *vasomotor tone* in the extremities, for enlarged *glands,* palpate the *abdomen,* test the *reflexes.* Use your *Ears:* Examine the *heart* and *lungs.* Take the *temperature, pulse, respiration* and *blood pressure.*

III. ROENTGEN RAYS. Should be taken while the patient is on the way to the ward, unless the patient is in *shock,* when immediate shock treatment takes precedence over everything else. *Skull plates* should be taken in all injuries, and whenever the diagnosis is not evident. Other plates as indicated.

IV. LABORATORY WORK. (1) *Gastric lavage* for all poisonings, and severe alcoholics. *Save the contents.* (2) *Catheterize* and examine the *urine* as soon as possible. If reducing substances or acetone are present, and in all diabetics, do a *blood sugar* at once.* (3) Do

* Coma due to hyperinsulinism is recognizable by blood sugar estimation.—[EDITORS.]

the *routine blood* (red and white counts, hemoglobin and smear). In the presence of infection take a *blood culture.* (4) Take blood routinely on non-traumatic cases for a *Wassermann* and *non-protein nitrogen* determinations. (5) Spectroscopy, icteric index, van den Bergh, electrocardiograph, blood CO_2 combining power, etc., when indicated.

V. LUMBAR PUNCTURE. Routine in *all injuries* (except during shock), *cerebral vascular accidents, convulsions,* in the presence of signs of *increased intracranial pressure* or *meningeal irritation,* and in all cases *where the diagnosis is obscure.* Note the *initial pressure, color of fluid, red* and *white cell count* and *Ross-Jones* protein test. Remove enough fluid for *Wassermann, total protein* and *gold solution examinations.* When indicated, do *smear, culture* and *chlorid* and *sugar determinations.*

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PAGET'S DISEASE (OSTEITIS DEFORMANS).

ANALYSIS OF 116 CASES.

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THE classic observations of Sir James Paget on osteitis deformans[1] have been confirmed and extended by subsequent investigations in various fields. Clinical reports on large groups of patients[2] have contributed in particular to the recognition and study of the disease in its early stages, an advance made possible by the introduction of roentgenologic examination. Biochemical research has provided a means of obtaining corroborating evidence in diagnosis through Kay's[3] discovery of the increased blood phosphatase activity in osteitis deformans. Extensive pathologic investigations, notably

those of Schmorl,[4] have facilitated the ultimate histologic diagnosis of the disease by establishing as characteristic a disordered "mosaic" architecture, resulting from the formation of irregular segments of lamellar bone, with prominent cement lines.[5]

Apart from their general interest, these advances have important implications in medical practice. It is now evident that the disease is not as rare as was formerly supposed but must be accounted among the more common primary affections of bone occurring after the third decade of life. The differentiation of Paget's disease from other diseases of bone, hyperparathyroidism for example, may be of vital importance in determining the course of treatment. The management of Paget's disease still presents many problems since treatment, except for palliative relief of pain in some cases, is unsatisfactory. The etiology of the disease remains unknown.

The observations recorded here are based chiefly upon the records of 104 cases of Paget's disease seen in the wards or outpatient department of this hospital from 1915 to 1935.* Of this number, 59 were seen from 1930 to 1934 inclusive, the total number of new patients treated during this period being approximately 200,000, of whom about 70% were over 30 years. Observations for a period of 5 years or longer were available in 26 cases. We had the opportunity to examine 77 cases of Paget's disease ourselves.

The diagnosis was established radiologically in every instance. With the exception of 3 very early cases, the lesions were sufficiently advanced to satisfy unequivocally currently accepted roentgenologic criteria of Paget's disease. In the early cases, the findings were limited to isolated areas of sclerotic condensation in a matrix of coarsely trabeculated bone. In addition to radiologic evidence, 41 cases presented deformities which made the clinical diagnosis obvious or probable. The phosphatase activity of the blood was determined in 76 patients[6] and found to be elevated in all but 1 early case.

Fifty-eight of the cases were males, 58 were females; 13 patients were negroes. No correlation between incidence and nationality or occupation could be established. No one station of life seemed to be particularly prone to the disease. In 4 instances, more than one member of the same family were found to be affected. In 1 case, 3 siblings and their mother presented the typical picture of the disease (Case 5, F. F.), in another 2 brothers and a son. The mother of a third case was shown to have osteitis deformans by radiologic examination elsewhere. Two of the cases in this series are brother and sister. Several other patients gave vague descriptions of other members of their families with moderate bowing of

* This study was made possible through the coöperation of the members of the medical, surgical and radiologic staffs. We are indebted particularly to Dr. W. W. Palmer and Dr. Ross Golden. We wish to express our appreciation also for the opportunity to examine 12 cases seen in other hospitals.

extremities or enlargement of the head, but these reports could not be investigated.

As in all previous studies,[2] the patients in this group were over 30 years of age when the disease was recognized (Table 1) with the

TABLE 1.—AGE INCIDENCE OF 116 CASES OF PAGET'S DISEASE.

Age in years.	25–29	30–39	40–49	50–59	60–69	70–79
Age when diagnosed, number of cases	1	6	22	34	40	13
Age at onset of symptoms, number of cases (27 cases asymptomatic)	2	9	29	35	12	2

exception of one patient who gave her age as 28. The figures relating to age when the first symptoms appeared are approximations only, as in some instances the onset was so insidious that the duration of symptoms could not be determined accurately; in others, it was not clear whether the symptom (pain, for example) should be attributed to Paget's disease or to coexisting pathology such as osteoarthritis or arteriosclerosis. No inference as to age at onset of the disease can be drawn from the age when symptoms first appeared, since the time which may elapse before bone lesions elicit symptoms varies widely in different patients. It is significant, however, that, so far as we have been able to determine, no authentic case of Paget's disease has been recognized in persons before the age of 25.

Twenty-seven cases had no symptoms or signs that could be referred to Paget's disease at the time the diagnosis was made. Skeletal changes were discovered fortuitously in the course of roentgenologic examination of the gastro-intestinal tract (12 cases), genitourinary tract (8 cases), paranasal sinuses (6 cases), or chest (1 case). In 12 of these patients subsequent radiologic examination of the skeleton showed fairly extensive Paget lesions which were entirely unsuspected by the patient or by the examining physician. There can be no doubt that a large proportion of cases of osteitis deformans escapes detection. Schmorl's systematic postmortem studies revealed an incidence of about 3% in persons over 40 years of age.[4]

In the 89 cases with symptoms referable to Paget's disease, within the limitations already alluded to, the course of the disease was usually so insidious that the patients did not apply for medical aid until many years after the onset of symptoms. Even then, in 25 cases, they consulted a physician primarily because of some unrelated disease. The initial manifestation of the disease appeared acutely in 18 patients, in the form of sharp pain (12 cases) or pathologic fractures (6 cases).

The initial and major symptoms of this group are summarized in Table 2. The most common first manifestation of the disease was

TABLE 2.—INITIAL SYMPTOM AND MAJOR SUBSEQUENT SYMPTOMS IN 116 CASES OF PAGET'S DISEASE.

	Initial symptom (number of cases).	Major subsequent symptoms (number of cases).
1. Pain back; hips; extremities	37	63
2. Headache	6	31
3. Deformities legs; spine; arms	17	48
4. Enlargement of skull	13	28
5. Fractures	6	16
6. Deafness	3	26
7. Difficulty in gait	5	38
8. Paresthesias	2	6
9. Vertigo	..	22
Asymptomatic	27	22

pain in the region of bone involvement, usually in the legs, lower back or hips. This was a dull ache, most frequently not sharply localized, usually worse after exercise and relieved by rest. Occasionally, the pain would occur at night. Varying degrees of stiffness in the joints were commonly associated with the pain. These complaints were generally considered "rheumatic" or "neuralgic" and often dismissed as due to "old age." The pain was rarely as severe or as generalized as in many advanced cases of hyperparathyroidism and more likely to mitigate or disappear spontaneously in the course of the disease. Definite bone tenderness was present in only 3 cases. Diffuse muscle pain and spasm were common accompaniments of deformities. Acute cramp-like muscle pain occurred most frequently in the calves of the legs. Thirty-one patients complained of pain in the head varying from an occasional headache, dull or throbbing in character, to the most excruciating recurring neuralgia. Many patients with obvious involvement of the skull had little or no headache.

No deformities whatever had been observed by the patient in 57 cases. Of these, in 45 instances no definite aberration from normal bone contours could be made out upon careful clinical examination of areas shown by Roentgen ray to be involved, sometimes quite extensively. This occurred most frequently when the pelvis and lower spine were the site of the lesion, less often when the bones of the extremities, more amenable to palpation, were involved. In only 17 patients had skeletal deformities advanced so far as to present the complete picture so graphically described by Paget (Fig. 1). The majority of cases (54) presented deformities but did not conform to the classic picture of the disease. Unilateral or bilateral bowing of the femora (usually with convexity of the lateral aspect), tibiæ (usually with convexity of the anterior aspect) or humeri were encountered, singly or in combination, with or without abnormalities of the spine and skull. Nineteen cases had markedly bowed extremities without obvious skull enlargement, 14 had massive heads without obviously deformed extremities. Eleven patients

had deformities of the radius or ulna, usually associated with changes elsewhere. In only 3 instances was involvement of the small bones of the hand or foot recognized.

Pain was usually present for some time before deformities were noted, but in 22 cases the appearance of deformities was preceded by no pain or by only slight pain. By the time any one bone was so extensively involved as to be obvious clinically, radiologic examination of the remainder of the skeleton almost invariably revealed lesions elsewhere. This obtained also for the tibiæ which appeared to be normal clinically in 16 cases presenting advanced deformities in other bones. While abnormalities of the tibiæ may be the first or



FIG. 1.—M. P. Advanced Paget's disease, showing marked asymmetric enlargement of the skull (64.2 cm.), with parietal bossing. An unusual feature is the involvement of the mandible, which is apparent.

only sign of the disease, and are easy to palpate, the importance of bowing of the tibiæ as an early clinical sign of Paget's disease has been overemphasized, we believe. Deformities in persons under 40 years of age are rarely due to osteitis deformans. But Paget's disease must be considered among the more common non-traumatic causes of deformities in extremities developing late in life.

Marked bowing of a long bone may lead to the development of numerous incomplete fissure fractures of its convex aspect (Fig. 2*a*). Pathologic fractures, characteristically transverse, usually follow (Fig. 2*b*). In 14 cases, fracture after little or no trauma had occurred, in 6 instances without preceding pain in the affected limb. Compression fractures of the spine, apparently asymptomatic, were discovered in the Roentgen ray films in 3 instances. Most frac-

tures healed firmly with abundant callus (Fig. 2c) usually within the period required for union of normal bone.

Fatigability and moderate general muscle weakness were common, particularly in patients with deformities of the lower extremities. As bowing with shortening of one leg progressed, limp developed (Fig. 3) and as deformities advanced, locomotion became more and more labored; 12 patients could not walk unsupported, some



FIG. 3.—L. M. Moderately advanced Paget's disease. To show characteristic posture noted in many cases where there is marked shortening of one leg.

could not even stand. Marked muscle atrophy and some decalcification of the bones due to disuse were common in such cases. For the most part, however, as Sir James Paget pointed out,[1] patients with osteitis deformans are able to support their weight in spite of extreme deformities of the lower extremities. In 7 cases, difficulties in gait became manifest in the absence of any bowing of the legs or were wholly disproportionate to the mechanical disability present. Such patients developed an uncertain, broad-based waddle and

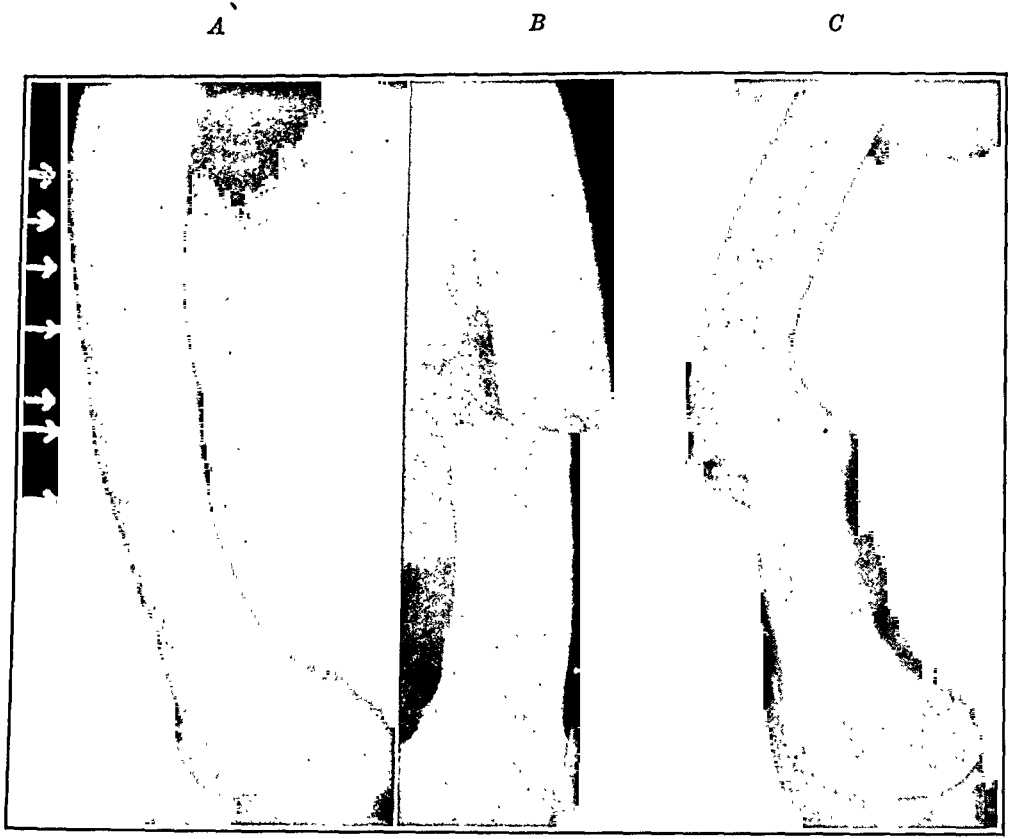


FIG. 2.—*A*, H. S. Left femur with numerous incomplete fissure fractures through the convex aspect. *B*, R. N. Left femur with a typical transverse fracture. *C*, R. N. Abundance of callus formation usually seen in healed fractures through Paget bone.

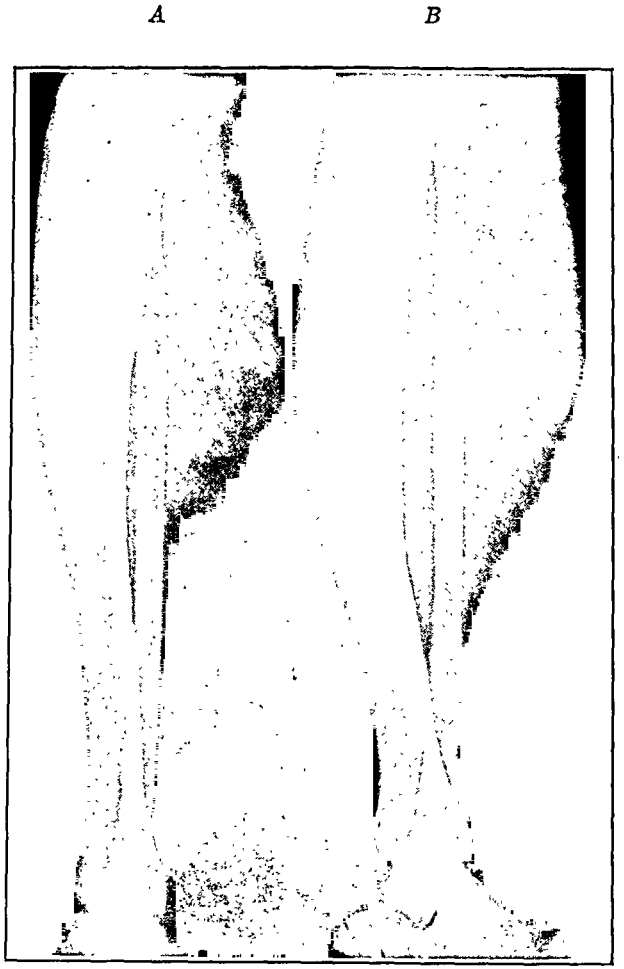


FIG. 4.—M. S. *A*, Lateral view of the right tibia in 1927. *B*, same in 1935. Note extension of the process distally, with increased expansion of the cortex and more marked bowing.

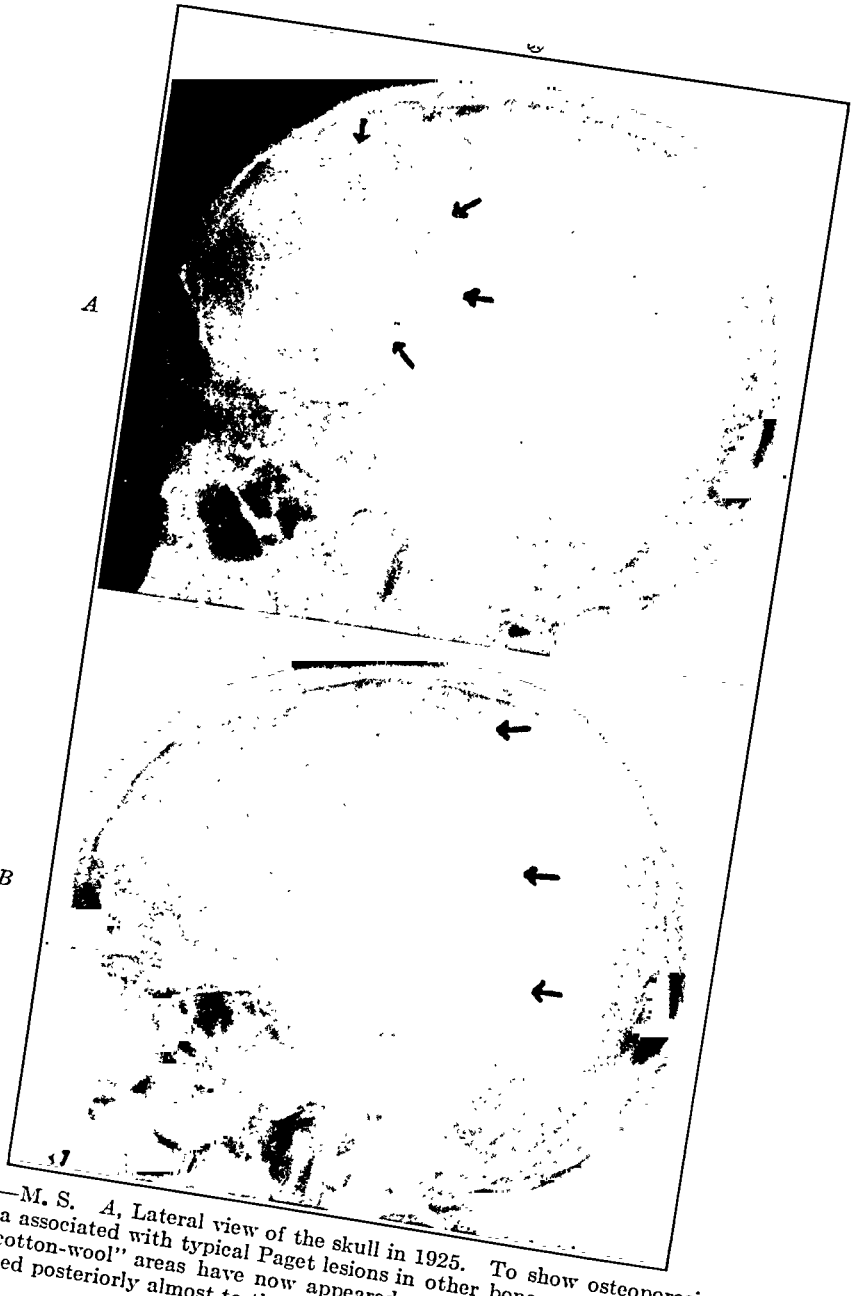


FIG. 5.—M. S. *A*, Lateral view of the skull in 1925. To show osteoporosis circumscripta associated with typical Paget lesions in other bones. *B*, same in 1935. Typical "cotton-wool" areas have now appeared. The osteoporosis circumscripta has extended posteriorly almost to the occiput.

characteristically progressed by supporting themselves on successive fixed objects in their paths. Incapacitation was likely to progress more rapidly and to become more complete when due to impingement of bone upon the cerebellum, spinal cord or spinal nerve roots than when due to bowing or other mechanical difficulties.

The infrequency of predominating psychic or neurologic symptoms has been commented upon many times, since contraction of the vertical diameter of the cranium[7] and of the lumen of the spinal canal and nerve outlets[8] may be striking. Two cases in this series had dementia, 2 others were paranoiac. As the skull was markedly involved in all these cases, there may have been some relation to Paget's disease. Symptoms suggestive of cerebellar ataxia, seen in some of our cases, may be inconspicuous despite roentgenologic evidence of marked cerebellar compression. Impairment of hearing was the most common manifestation of cerebral nerve involvement. Twenty-six patients complained of deafness but in many instances this was the result of infection or, where audiograms were obtained, was shown to be due primarily to faulty bone conduction. Impairment of vision was not uncommon but was the result of optic atrophy in only 4 instances. For the most part, changes in the eyegrounds were secondary to sclerosis of the retinal vessels which was present in some degree in most patients. Case J. R. illustrates the occasional association of angioid streaking with Paget's disease. Numbness and tingling of the feet was the initial symptom in 2 cases. How much of the disability and pain observed in many cases should be attributed to nerve impingement is uncertain.

Our series is unusual in that sarcomatous degeneration was not observed. One case died of sarcoma but this was thought to be unrelated since postmortem examination showed the tumor to be of the reticulum cell type. Another case, suspected of early sarcomatous changes, is being followed.

Roentgenologic Considerations. The importance of roentgenographic examination is illustrated by the fact that clinical evidence sufficient to warrant the diagnosis of osteitis deformans was absent in almost two-thirds of our cases. In all cases, radiologic study was considered essential for confirmation of the diagnosis as well as for determining the extent and character of the pathology in various bones. Recapitulation of the characteristic and well-known roentgenographic features of Paget's disease is unnecessary here.[9] Only specific details will be considered, particularly those relating to bone changes disclosed by follow-up studies, in some instances of 10 years' duration.

In 14 cases the lesions appeared to be localized to a single area. Of these, however, 8 were in the skull or pelvis and involved at least two adjacent bones, so that the term "monostotic" could be applied properly to only 6 cases. Early lesions in a long bone were

confined almost invariably to one end of the shaft, the remainder of the bone being apparently normal (Fig. 4); or both ends of the shaft were involved and in the course of time appeared to converge toward the midshaft. In the pelvis, early lesions were seen most frequently in the area comprising the bodies of the ischium, pubis and ilium, medial to the acetabulum. In many of the early cases, only one side of the pelvis was involved. The marked deformities seen in some pelves due to upward and inward protrusion of the heads of the femora, as well as the bowing of weight-bearing long bones, reveal the softening of bone which may take place in this disease. In many instances, different bones or even different areas of the same bone presented strikingly varied lesions ranging from local or regional osteoporosis with coarsened trabeculations to dense osteosclerosis. In several cases, the development of sclerosis in striated areas could be demonstrated in subsequent films. Osteitis deformans may become arrested at any stage as shown in Case M. S., where the lesion in the pelvis remained practically stationary in the coarsely striated stage for 10 years. It would seem hazardous, therefore, to draw from a single roentgenogram, any conclusions as to the activity of bone changes or to predict the course of the disease.

TABLE 3.—INCIDENCE OF INVOLVEMENT OF DIFFERENT BONES IN 116 CASES OF PAGET'S DISEASE.

Skeletal distribution.	Number studied.	No. not involved.	No. showing involv.	Early changes	Advanced changes	Bilateral involv.
Skull*	105	23	82	17	65	
Scapula	63	45	18	4	14	8
Clavicles	63	48	15	6	9	10
Ribs	63	55	8	4	4	3
Cervical spine	46	41	5	..	5	
Dorsal spine	64	38	26	8	18	
Lumbosacral spine	92	41	51	17	34	
Pelvis	101	11	90	10	80	
Humerus	63	26	37	10	27	11
Radius	27	20	7	6	1	
Ulna	27	22	5	4	1	
Hands	8	7	1	1		
Femur	91	32	59	8	51	33
Patella	60	59	1	1		
Tibia	63	29	34	7	27	14
Fibula	63	59	4	4	..	1
Feet	6	5	1	1		

* In 3 cases, osteoporosis circumscripta of the skull was the only skull manifestation, with typical Paget changes elsewhere.

In the skull, early "cotton-wool" changes were seen most frequently in the frontoparietal or frontal region, rarely in the occipital region alone. Involvement of the base of the skull (7 cases) or of the facial bones (6 cases) was unusual and was never seen unless advanced lesions of the cranial vault were present. Osteoporosis circumscripta of the skull[10] was observed in 10 cases, together with a "cotton-wool" appearance of the calvarium (7

cases) or as the only skull change associated with Paget's disease elsewhere. Follow-up studies showed that typical lesions of osteitis deformans developed in the osteoporotic area which itself expanded during this period (Fig. 5; see Ref. 10 for other examples). Osteoporosis circumscripta should not be confused with the multiple rounded areas of local osteoporosis often surrounding "cotton-wool" lesions in the calvarium.

Generalized decalcification of the skeleton, of the type seen in hyperparathyroidism, was not encountered. Varying degrees of osteoporosis were seen associated with coexisting marked arthritis or where the patient was confined to bed as the result of fractures or deformities. Cystlike changes, thought to be fatty-marrow spaces,[5] were seen occasionally at the proximal ends of the femora or humeri. Fractures, described above, occurred most frequently in the femora, humeri and tibiæ.

The incidence of osteitis deformans in various bones in these cases is summarized in Table 3. The pelvis, skull, femur, humerus, lumbosacral spine and tibia were most commonly involved.

Biochemical Considerations. The blood constituents of chief interest are those most intimately concerned with bone metabolism, so far as they are known: calcium, inorganic phosphorus and phosphatase. As reported in most recent studies,[11] the serum calcium and inorganic phosphorus are within normal limits, whereas the blood phosphatase activity is increased. Of the 78 cases examined, the serum calcium was between 9 and 11 mg. % in 69, between 11.1 and 11.5 mg.% in 8. In 1 patient repeated values over 12 mg.% were obtained, apparently due to complicating factors and not to the localized Paget lesion present.[12] Recent investigation warrants the conclusion that the diagnosis of uncomplicated Paget's disease is doubtful where repeated analyses by competent observers show elevated serum calcium values.

The serum inorganic phosphorus in the 77 cases examined was not less than 2.7 mg.% or more than 4.2 mg.% except where associated renal impairment caused retention. With the exception of 1 early case, the determination of serum phosphatase activity in 76 patients uniformly yielded values exceeding 4 Bodansky units (the maximum for normal adults[11d] by Bodansky's method). Our results favor the view that the level of blood phosphatase activity in this disease is determined largely by the extensiveness of skeletal involvement, as shown by Roentgen ray (Fig. 6). In our 5 most advanced cases, the values ranged from 130.3 to 59.5 Bodansky units. In our 10 cases presenting only early localized lesions, the blood levels ranged from 8.3 to 4.5 Bodansky units, with the exception of 1 case in which a value of 1.8 Bodansky units was obtained. In 13 of 15 cases presenting advanced involvement of one area with early lesions elsewhere, the spread was between

20.8 and 4.1 Bodansky units. In the 2 remaining cases, in which the skull was maximally involved, the values were 53.6 and 49.1 Bodansky units. In the remaining group of cases, the most common type encountered, presenting advanced polyostotic lesions, there was a diffuse scatter over a very wide range: 120.6 to 9.7 Bodansky units. In this group particularly, disproportionately high values may be found in cases presenting an unusually rapid course and unexpectedly low values may be encountered in cases clinically quiescent. It would appear, therefore, that the rate at which the

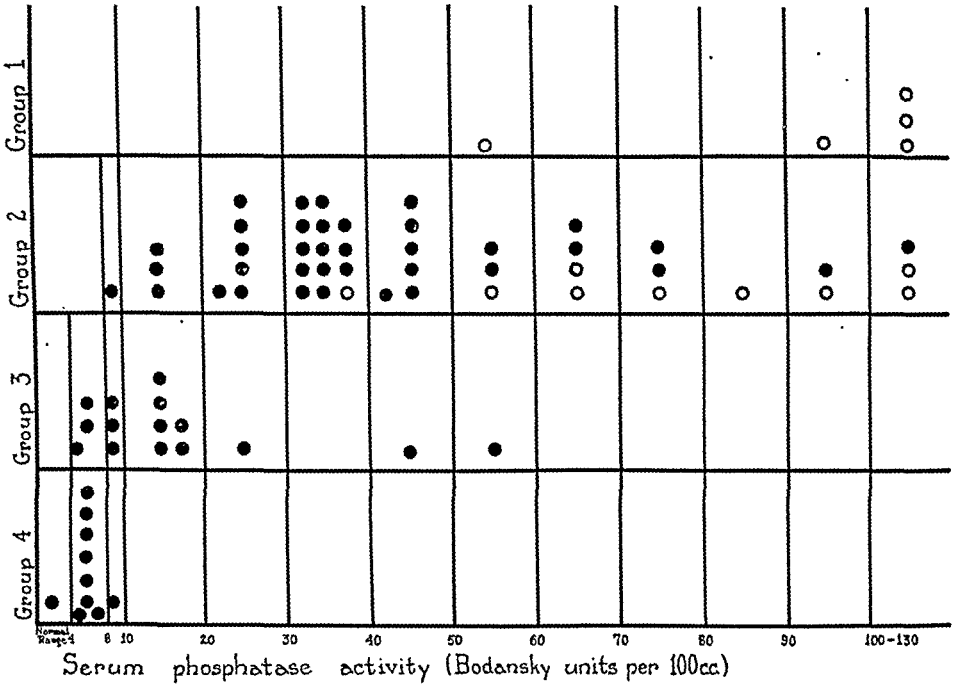


FIG. 6.—Distribution figure to show the correlation between serum phosphatase levels and extensiveness of bone involvement in 76 cases of Paget's disease. The cases are divided arbitrarily into four groups, according to the extent of bone involvement as shown by Roentgen-ray. Group 1 comprises the most advanced cases, Group 4 those with early localized lesions (see text). The hollow dots represent cases progressing relatively rapidly.

disease progresses may affect the level of blood phosphatase activity in osteitis deformans[2c,2d,11d] and that the determination is of some value in prognosis.

A significant finding not emphasized in the literature is the constancy of the serum phosphatase level in many cases of Pagets' disease when determined at intervals (see case histories). In exceptional instances, however, wider variations were encountered as in Case J. W., whose blood showed 94.3 Bodansky units in 1934 and 60.6 Bodansky units in 1935. As is well known, markedly increased blood phosphatase activity is not specific for Paget's

disease but may be encountered in several conditions where there is an increase in processes leading to bone formation,[13] or with liver damage.[14] Its determination may give valuable corroboratory evidence in diagnosis and also information as to activity, but it is of no value in differentiating from osteoplastic carcinoma metastases, particularly in carcinoma of the prostate.[12] While sometimes helpful in early diagnosis, often, in our experience, the bone lesions must be sufficiently far advanced as to be obvious radiologically before the increase in serum phosphatase activity is unequivocal.

Five case reports, each representative of a group of patients, have been selected for summarization. The cases illustrate how widely the course of the disease may vary, depending in large part upon the purely mechanical effect of Paget lesions as determined by their location, extent, stage and rate of development. Cases 1 (M. S.) and 2 (L. M.) represent the most common types encountered, in which deformity or pain was the chief complaint. Both patients presented very similar findings at the time of their first examination 10 years ago. M. S. has remained free of serious symptoms whereas L. M. has become completely disabled. M. S. is interesting also because of the associated osteoporosis circumscripta of the skull. Case 3 (J. R.) illustrates the course of the disease when neurologic symptoms due to compression of the spinal cord, brain or nerve roots predominate. In Case 4 (A. O.), the clinical course was determined by the occurrence of fractures and their complications. This was one of the few instances where the differentiation from hyperparathyroidism offered any problem. Case 5 (F. F.) is typical of a number of patients in whom deafness is the most distressing symptom. The case is of special interest because of the unusual familial incidence of Paget's disease.

Case Abstracts. CASE 1.—M. S., an American housewife, aged 43, was admitted to this hospital in 1925 because of acute appendicitis. Appendectomy was performed, with uneventful recovery. An incidental finding was an irregular swelling and anterior bowing of the left tibia suggestive of Paget's disease. No other deformities were demonstrable clinically. The bowing of the left leg, first noted by her in 1918, had slowly progressed. She had never had pain in that leg or elsewhere, nor were other symptoms or signs of osteitis deformans present. She was the only member of the family affected.

The Wassermann reaction of the blood and urine analyses were negative. Radiologic examination disclosed characteristic coarse trabeculations and expansion of the left tibia, pelvis, sacrum, distal third of the right femur, upper third of the right tibia, head of the right humerus, and second metacarpal of the left hand. The skull showed only an area of osteoporosis circumscripta in the right frontoparietal region (Fig. 5*a*). The lumbar and dorsal spine, thorax, shoulder girdle, left femur and fibulæ were normal. Reëxamination of the skeleton in 1927 disclosed no apparent change except the development of a few sclerotic islands in the area of osteoporosis circumscripta. Reëxamination in 1935 revealed extension of the area of osteoporosis circumscripta and an increase in "cotton-wool" islands within it (Fig. 5*b*). The tibiæ were more bowed, especially on the right side which

now showed involvement of the upper two-thirds and increased cortical thickening and expansion. In the right femur the changes now extended to the neck. There was a slight increase in the process in the pelvis without sclerosis. There was no definite alteration in the appearance of the spine. Examination of the blood (1934) showed serum calcium 10.2, serum inorganic phosphorus 3.8, serum non-protein nitrogen 32 mg. per 100 cc., and serum phosphatase 34.6 Bodansky units per 100 cc.

Her course has been practically asymptomatic. Her legs began to tire easily in 1927 and this has led to some restriction of activity in recent years. Since 1930, the right tibia has become progressively bowed anteriorly. In 1934, she experienced occasional cramps in the calf muscles. Apart from this she has been entirely free of pain, her gait is affected but little, her head has not increased in size, she has had no headache, hearing and vision are unimpaired. She is (1935) an alert woman who performs her daily household activities without difficulty. She presents no clinical stigmata of Paget's disease except bowed tibiæ.

CASE 2.—L. M., a Jewish male, mechanic. There is no familial or childhood history of bone disease. In 1925, when 43, a friend pointed out a slight bowing of the right leg. The leg began to ache several months later. He went to the Neurological Institute, where radiologic examination (Dr. C. W. Schwartz) revealed advanced Paget's disease of the right femur and of the skull, with earlier lesions in both humeri, scapulæ, the left clavicle and left femur. Reëxamination in 1927 showed additional changes in the pelvis. The Wassermann reaction of the blood was negative. Examination of red cells, hemoglobin, leukocytes, calcium, urea, uric acid and sugar in the blood gave normal values. The urine was negative.

Because of continued severe pain in the right leg and lower back, he applied to our outpatient department in 1930. Limp had developed as a result of increased bowing and shortening of the right leg. He was treated with a variety of glandular preparations, baking and massage, and various analgesics without relief. His course since then has been one of progressive and relatively rapid incapacitation. Pain and increasing difficulty in gait have made work impossible since 1932. A rounded dorsal kyphosis, enlargement of the skull and bowing of the left femur, all first noted in 1932, have increased markedly. His stature has decreased from 5 feet 7 inches to 4 feet 6 inches. The deformities of the femora have made walking so painful, labored and fatiguing that, even with the help of a cane, he can negotiate only short distances. Hearing is impaired on the right side, audiometer readings indicating moderate nerve deafness. The tibiæ show no changes clinically. He has had no headache. Radiologic examinations have shown increasing involvement of the skull, with encroachment upon the bones at the base, and advanced lesions particularly of the pelvis, spine and both femora. There is marked arteriosclerosis. His eye grounds also revealed sclerotic vessels and in addition suggestive angioid streaking.

A course of radiotherapy to the involved bones has relieved his pain considerably. There has been no significant change in blood values as a result of treatment. In September, 1934, chemical examination showed serum calcium 10.7, serum inorganic phosphorus 3.2, serum non-protein nitrogen 32 mg. %; serum phosphatase 122.2 Bodansky units per 100 cc. In March, 1935, the values were 10.2, 3.4, 23 and 116 respectively.

CASE 3.—J. R., a Jewish housewife, aged 54, was admitted to this hospital in October, 1934. Her familial history was irrelevant, except for a paternal uncle who was said to have had deformities suggestive of Paget's disease. She had been well until 1924 when she complained of occasional attacks of "neuritis" in the shoulders and legs, accentuated by exercise, and relieved by rest. In 1927 she began to have intermittent occipital headaches of "burning" character. These have increased progressively

in severity and duration and for the past 5 years have been almost unremitting. She noticed enlargement of the skull about this time. Radiographs of the skull in 1928 disclosed Paget's disease. In 1929 she noted bowing of the legs and complained of pain in the knees and in the calf muscles of both legs. In 1930 increasing kyphosis of the upper dorsal spine developed, with tenderness of the spine between the shoulder blades. About this time her gait became unsteady. She fell several times, on one occasion fracturing her right arm. The uncertainty in gait was not due to weakness but to loss of sense of balance. For a time she was able to walk by steadying herself on fixed objects, but has spent most of her time in bed in recent years. By 1930 her head was so large that she had difficulty getting hats to fit her. In 1931 she began to complain of dysphagia and regurgitation and has had to limit her diet to soft foods since then. She attributes a loss of 30 pounds in the 2 years following to difficulty in swallowing. This has improved in the last 2 years and she has recovered most of the weight lost. In 1931 photophobia developed, without impairment of vision. She has had to wear dark glasses for several years. Deafness of the left ear, with occasional tinnitus, has been noted since 1932. In 1932 she complained of paresthesias of the fingers of both hands and found that she was unable to tell whether she had succeeded in grasping small objects unless she looked at her hands. In 1933 her speech became thick. She has been orthopneic for 2 years. Her presenting symptom when first seen was headache.

On admission she was markedly deformed and wholly incapacitated but withal cheerful and mentally alert. The skull was markedly and asymmetrically enlarged with a prominent bulge in the left parietal region. The neck was short and almost immovable, the chin resting on the sternum. There was a kyphoscoliosis of the spine with an angular deformity in the upper dorsal region. The thoracic cage was fixed, the clavicles thickened and protruding. Both femora, humeri, radii and the left ulna were thickened and deformed. The tibiæ appeared to be normal. Examination of the eyes showed irregular horizontal and vertical nystagmus with weakness of the right inferior rectus muscle. There was no papilledema, temporal pallor of the disks was within normal limits. Retinal vessels were sclerotic. Typical angioid streaking of the retina was present. Examination of the chest, heart and abdomen disclosed arteriosclerotic heart disease with moderate passive congestion of the liver.

Neurologic examination showed a positive Romberg test, the patient being unable to stand without support. Deep reflexes could not be elicited even with reinforcement. Suggestive Babinski and Chaddock responses were obtained on both sides. There was considerable uncertainty in the heel-to-knee test. There was a loss of vibratory sense over both lower extremities and pelvis, preserved over the upper extremities and spine. Abdomen reflexes were absent. The muscles of both legs were markedly atrophied. There was no apparent weakness or atrophy of the tongue, palate or pharyngeal muscle groups. Attempts to drink fluids, however, revealed difficulty in swallowing. The findings suggested encroachment upon the brain and spinal cord.

Radiologic examination showed marked involvement of the skull including the bones at the base. The floor of the skull was convex ("convexobasic"). The vertical diameter of the skull and the dimensions of the cerebellar fossa were markedly diminished. The pelvis, spine, femora and right humerus were involved. The tibiæ were normal. Marked arteriosclerosis was present.

The visual fields were contracted, suggesting impingement of bone upon the optic foramina but stereoscopic films of the optic canals revealed these to be normal in size and contour. Fluoroscopic examination of the esoph-

agus showed no abnormality of lumen or contraction. The dysphagia appeared to be due to difficulty in initiating upward and forward movements of the tongue and larynx as the barium bolus slipped backward from the base of the tongue. It was felt that this might be due to a central lesion.

The Wassermann reaction of the blood was negative. The red cells, leukocytes and hemoglobin of the blood were normal. Examination of the urine was negative. The serum calcium was 10.6, serum inorganic phosphorus 3.7, non-protein nitrogen 28 mg. %; the serum phosphatase was 117.5 Bodansky units per 100 cc.

CASE 4.—A. O., an American woman, aged 60, was admitted to this hospital in October, 1933, because of inability to stand since sustaining a fracture of the right femur 2 years before. There was no familial history of bone disease. Her history was irrelevant until 1928 when she complained of "rheumatic" pains in the lower back, hips and right leg, associated with stiffness and unusual fatigue. In 1929, she noted increasing deafness on the right side with occasional tinnitus. In 1931, she fractured her right femur after a slight fall, with firm union in 6 weeks. Radiologic examination revealed extensive skeletal changes interpreted as Paget's disease, though with marked associated decalcification. Three months after the first fracture, while on crutches, she fell and sustained another fracture of the right femur. The fracture healed well in 2 months. Nevertheless, she was confined to bed or to a wheel chair for the next 2 years because the right leg had become too weak to support her. There was some increase in the size of the head in the past year. There was practically no pain, no headache, no vertigo. No obvious deformities had developed. Vision was unimpaired.

Examination showed a well-preserved, rather obese woman. The positive findings were a moderate enlargement of the head, some impairment of hearing, marked atrophy of the muscles of the right leg and generalized arteriosclerosis with moderate elevation of blood pressure. There was some thickening of the distal end of the right femur but no other deformities were present. Neurologic examination failed to show any abnormalities. Radiologic examination revealed advanced Paget's disease of the skull, pelvis, spine, right femur, right tibia and right humerus. The pelvis, spine and bones of the right leg showed, in addition, a degree of osteoporosis unusual in uncomplicated Paget's disease. It was felt that this was due to disuse. Marked arteriosclerosis was present.

The Wassermann reaction in the blood was negative. The red cell, hemoglobin and leukocyte content of the blood were normal. Urine analysis was negative. On October 3, 1933, the serum calcium was 10.1 mg. %, serum inorganic phosphorus 2.9 mg. %, serum phosphatase 88.7 Bodansky units per 100 cc. Three days later, the values were 10.3, 3.1 and 88.1 respectively. Calcium and phosphorus balance studies were carried out. She was placed on a neutral ash diet approximating 100 mg. calcium and 400 mg. phosphorus a day (determined by analysis of aliquots) for 6 days. The output in stool and urine was then estimated for 2 three-day periods. Her average daily output of calcium on this regimen was 0.252 gm., of which 32% appeared in the urine. The average daily negative calcium balance was 0.147 gm., the average daily negative phosphorus balance was 0.175 gm. These values fall within the range observed in normal persons on similar diets.

It was felt that the possibility of hyperparathyroidism, which had been considered, was excluded. In the belief that the weakness of the right leg, her presenting problem, was due to secondary muscle atrophy and osteoporosis, she was given a high calcium diet with viosterol and the right leg was massaged and exercised regularly. In a few months she was able to

get about in a "walker" at first supporting her weight largely with her arms. By May, 1934, she could support her weight on her right leg without difficulty. Muscle atrophy was less marked. Roentgen rays showed slight increase in density of the decalcified bones. The serum calcium was 10.1 mg. %; serum inorganic phosphorus, 3.5 mg. %; serum phosphatase 91.9 Bodansky units per 100 cc. At the suggestion of Dr. C. R. Murray broad based tripod crutches were gradually substituted for the "walker." In the course of the next year she could get about surprisingly well. In 1935, the serum calcium was 10.2 mg. %, serum inorganic phosphorus 2.5 mg. %, serum phosphatase 90.4 Bodansky units per 100 cc.

CASE 5.—F. F., an American salesman, aged 69, came to this hospital in June, 1934, because of deafness. His family history was extraordinary. His mother was described as having had a very large head, together with bowing of the legs which had developed after the age of 45. A sister had advanced Paget's disease, verified by radiologic examination. A brother, now 80, presents a classic picture of Paget's disease with marked bowing of the legs, difficulty in gait, moderate enlargement of the skull and deafness.

The patient noted an increase in the size of his head 20 years ago. For many years his hats have been specially made for him. In 1925, bowing of the right femur developed, subsequently causing shortening of the right leg and limp. This has not proven a serious handicap, however, as it has been his custom for years to walk several miles a day without the use of a cane and without fatigue. Since 1917 deafness has been his chief problem. There is a total loss of hearing on the right side and marked impairment on the left, which forced him to give up his work. His skull had been Roentgen rayed several years before; advanced Paget's disease was found. He denied ever having had pain, vertigo or headache.

Examination disclosed a remarkably well preserved man. His skull was markedly enlarged with prominent bulging of the parietal bones on both sides, separated by deep fissures from the domelike vertex; The skull measured 26½ inches in its greatest circumference. The right femur was bowed. No other abnormalities, except the deafness, were noted. The tibiæ appeared to be normal. Examination of the blood showed (mgm. per 100 cc.) serum calcium 10.7, serum inorganic phosphorus 3, serum non-protein nitrogen 36; serum phosphatase 72.6 Bodansky units per 100 cc. In March 1935 the values were 11, 3.2, 37 and 77.6 respectively.

Differential Diagnosis.—Even early localized Paget's disease, without clinical manifestations, presents so distinctive a roentgenologic picture that there is usually no question as to diagnosis. Our most common problem was to distinguish osteoplastic skeletal metastases secondary to prostatic carcinoma from sclerotic Paget lesions. While the clinical findings and course usually revealed the primary tumor, in occasional cases rectal and cystoscopic examination were equivocal and urologic symptoms, loss of weight and anemia were absent or mild. The radiologic manifestations in both diseases may be very similar but, as Sutherland[15] pointed out, metastases cause no expansion of bone contours, coarse striations are never seen, the skull changes when present do not show a typical "cotton-wool" appearance and osteolytic lesions are usually discernible somewhere in the skeleton. The serum phosphatase activity may be as high in cases with extensive osteoplastic skeletal metastases as in advanced Paget's disease, the serum calcium and

phosphorus remaining within normal limits.[12] Osteoplastic metastases arising from sites other than prostate gland did not present any difficulty in diagnosis.

There was rarely any question as to differentiation of osteitis deformans from generalized osteitis fibrosa cystica (hyperparathyroidism). The clinical findings and course are usually sufficiently diverse to distinguish the advanced forms of these diseases. In classic hyperparathyroidism, generalized decalcification and bone cysts, together with hypercalcemia, hypophosphatemia and a marked negative calcium and phosphorus due to loss in the urine are characteristic findings.[16] The blood phosphatase activity is consistently elevated in hyperparathyroidism with extensive skeletal changes, but rarely exceeds 10 times the normal maximum. In remission, however, whether the result of surgical removal of parathyroid tumors or occurring spontaneously in the course of the disease, recalcification, particularly of large cystic areas, may produce a roentgenographic picture somewhat similar to Paget's disease. In this stage, moreover, the serum calcium and phosphorus are usually normal, the calcium and phosphorus balance is positive or within normal limits and the serum phosphatase may still be somewhat elevated.

The few cases of tertiary syphilis with bone involvement (commonly of the tibiæ and clavicles) seen at this hospital in the last 10 years did not present any serious problem in diagnosis. The radiologic features of proliferative luetic periostitis[17] differ markedly from those of Paget's disease. Only 7 of our cases of osteitis deformans had a positive Wassermann reaction in the blood and in 5 of these clinical manifestations of syphilis were present.

Melorheostosis[18] begins in younger individuals, is unilateral and usually involves the long bones of a single extremity, often including the hands. It is a form of osteosclerosis which produces an expansion with undulating contour of one aspect of the cortex. Involvement of the skull has not been described.

Three cases of leontiasis ossium were encountered.[19] The patients were less than 30 years of age and all stated that the deformity of the face had been present since childhood. The hyperostosis was confined to the facial bones in 2 instances, with encroachment upon the frontal bones and base of the skull in the third case. The remainder of the skeleton was not involved. The serum phosphatase was 2.8 and 3.5 Bodansky units per 100 cc. in the 2 cases investigated. The serum calcium and inorganic phosphorus were also normal.

Bowing of the tibiæ due to rickets acquired in childhood is readily distinguished from Paget's disease. Garrés' sclerosing osteomyelitis,[20] osteopetrosis,[21] hyperostotic meningiomas,[22] and cases of neurofibromatosis[23] or of yaws[24] with bone involvement may simulate superficially certain aspects of Paget's disease.

Management. The treatment of Paget's disease is symptomatic. Relief of pain by ultraviolet light, by administration of calcium, parathormone, viosterol and by acidotic salts such as ammonium chlorid has been reported.[25] Several of our patients had received one or more of these agents but in every instance without benefit or with transient and apparently subjective relief only. Beneficial effects have been reported also for arsenic,[2c] dried suprarenal extract by mouth[2d] and parenteral administration of extracts of adrenal cortex,[26] with which we have had no personal experience. The only unequivocal, although often temporary, relief of pain in our cases, apart from analgesics, was obtained in some patients by Roentgen therapy to the affected bones. In 30 cases treated with relatively small doses, the best results were obtained where the pain was localized to non-weight bearing bones. Headache and vertigo were helped in 4 cases by radiotherapy to the skull. In the evaluation of our results, as well as those reported by others, it should be kept in mind that spontaneous remissions of pain in Paget's disease are not uncommon.

Where unusual decalcification and muscle atrophy due to disuse had developed, high calcium diets with calcium and viosterol by mouth, together with carefully graduated exercises were instituted (see Case A. O.). Built-up shoes facilitated walking when limp resulted from shortening of one leg due to bowing. The selection of proper hearing appliances proved a boon when deafness was the presenting complaint.

Since spontaneous remission of pain and arrest of the process are not uncommon, this possibility should be held out to all patients. The probability of very slow extension of the disease or quiescence would appear to be greater when the elevation of blood phosphatase is inconsiderable.

Etiology. The prevailing opinion appears to be that Paget's disease is the result of some local disturbance in bone metabolism, the immediate cause of which is unknown. The preponderance of evidence, pathologic, clinical and biochemical, indicates that Paget's disease is not a generalized systemic disease, infectious or endocrine in nature. As in all previous reports, our cases did not show fever, cachexia, secondary anemia, leukocytosis or an increased erythrocyte sedimentation rate, where this was investigated, except when obviously due to coexisting pathology. Definite evidence of parathyroid overfunction was not observed in any case. Postmortem examination in 3 of our cases revealed parathyroid glands normal in size and histologic structure. There is no reason to consider syphilis or trauma as etiologic factors. The increase in phosphatase activity of the blood in osteitis deformans is probably a result and not the cause of the disease (Kay). The occurrence of Paget's disease in several members of the same family is exceptional and it is

doubtful that heredity plays a significant rôle in most cases. Neurotrophic and localized chronic inflammatory processes have been considered as etiologic factors. The frequent association of arteriosclerosis with Paget's disease has suggested that sclerosis of the nutrient arteries may be a factor in causation.[27] Pathologic demonstration is lacking, however. The lesions resulting from obliteration of nutrient arteries as observed clinically or experimentally do not resemble Paget bone, which is often conspicuously hyperemic in the presclerotic stage ("spongy hyperostosis," Wilks). The rarity of involvement of the small bones of the hands and feet, particularly exposed to occlusion of the peripheral circulation, would also seem to be inconsistent with this view.

Summary. 1. Observations on 104 cases of Paget's disease seen at the Presbyterian Hospital from 1915 to 1935, and 12 cases seen elsewhere are summarized. Osteitis deformans is among the more common primary bone diseases in patients over 30 years of age.

2. The diagnosis in all cases was based upon typical Roentgen-ray findings. Twenty-seven cases presented no symptoms or signs referable to Paget's disease, the lesions being discovered incidentally by Roentgen ray while examining other systems. In only one-third of the cases were the clinical findings sufficiently definite to warrant the diagnosis clinically. The large majority of cases were not advanced so far as to present the classic picture of osteitis deformans when first examined.

3. There was equal distribution of the sexes. With one exception, all patients were over 30 years of age. Familial incidence was recorded in 4 cases.

4. The incidence and characteristics of the initial and major subsequent symptoms and signs in this series of cases are outlined.

5. Five representative case histories are presented to show how widely the course of the disease may vary, depending in large part on the location, extent, stage and rate of development of the Paget lesions. In 2 cases, the clinical and radiologic changes over a 10-year observation period are contrasted.

6. The incidence of bone involvement, sites of predilection of early lesions in various bones and the nature of changes observed in follow-up studies, as shown by Roentgen ray, are discussed.

7. The serum calcium, inorganic phosphorus and phosphatase activity were determined in over 70 cases. The serum calcium and inorganic phosphorus were consistently normal in uncomplicated cases. With the exception of 1 early case, the serum phosphatase consistently exceeded 4 Bodansky units per 100 cc., reaching values over 100 Bodansky units in advanced cases. Our results favor the view that the blood phosphatase activity is roughly proportionate to the extensiveness and activity of the Paget lesions. The phosphatase values in any one case were usually remarkably

constant over long intervals. High blood phosphatase values are found in other bone diseases, particularly osteoplastic prostate metastases. In most instances, the radiologic diagnosis was obvious before the rise in blood phosphatase was striking.

8. The differentiation of Paget's disease from osteoplastic carcinoma metastases, hyperparathyroidism, bone syphilis, leontiasis ossium, melorheostosis and other conditions is briefly discussed.

9. The symptomatic treatment of osteitis deformans is considered, with particular reference to alleviation of pain by radiotherapy over the affected bones.

10. Various theories as to etiology are mentioned. Clinical or laboratory evidence for infection or endocrine disturbance was lacking in our cases. Postmortem examination in 3 of our cases revealed no gross or microscopic abnormalities of the parathyroid glands.

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A PREVIOUSLY UNDESCRIBED GRANULE WITHIN THE LYMPHOCYTE.

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In a recent study of the differential characteristics of blood cells when stained supravitally,[12] casual note was made of certain structures which appear in the cytoplasm of a significant and fairly constant percentage of the circulating lymphocytes. Further study of these bodies confirmed this original finding and suggested elaboration of their characteristics.

For a long time subsequent to the initial examination of blood with the microscope, lymphocytes were regarded as non-granular cells and classified as such by Ehrlich.[22] Schilling[28] and Virchow[31] have spoken of the lymphocyte as being a homogeneous globule. In 1902, Michaelis and Wolff[22] described the presence of certain granules within the spongioplasm of many lymphocytes. These were termed by Ferrata,[22] "plasmasomes," but have since been named "azure granules" as they take a bright red stain with the azure component of the Romanowsky dyes. They are not visible in the unstained state and are probably not stained by the supravital dyes.[27,4] Altmann in 1890, utilizing an acetic acid free fixative, observed the presence of certain cytoplasmic filaments which had previously been vaguely described in many different cells (Flemming, Maggi, etc.).[6] In 1899, Benda gave these structures the name "mitochondria" and they were further studied and established as normal constituents of the living cell by Schridde.[18,24] Additional investigation by Cowdry[5] has identified these structures as a cyto-

plasmic feature of the lymphocyte and has exhibited their specificity for the dye, Janus green. Sabin[27] and many others[8] have demonstrated the presence of certain bodies comprising the "segregation apparatus" of the lymphocyte. These are found in the viable cell only, vary in number, are moderately refractile, and are stained specifically with neutral red.[13]

Other than the three structures described, there has not been recorded any regularly appearing "granule" in the lymphocyte. The literature is, however, replete with descriptions of intra-cytoplasmic bodies; some of which appear solely in lymphocytes, whereas others are not specifically noted as occurring in these cells alone. Russell[20] observed acidophilic bodies within disintegrating plasma cells which finally were extruded as a result of rupture of the membrane. Hammar[21] in 1912 identified certain droplike inclusions of lipoid nature in the cytoplasm of the occasional lymphocyte.

Various authorities have commented upon the presence of small dark bodies located usually in the nuclear indentation[7,20,21] known as centrioles and stained with iron hematoxylin after the usual fixation. Large, so-called Foá-Kurloff[14] bodies have been demonstrated in the lymphocytes of older guinea-pigs, but apparently not in human blood. Cesaris-Demel[20] mentioned the presence of large, sudanophilic lipoid bodies within the cytoplasm of the component leukocytes of purulent material. Lewis and Lewis[17] noted the appearance within lymphocytes of tissue cultures of one or two small refractive granules, which did not change shape, size, or position and took the usual fat stains. These occurred predominantly in degenerating cells. Sabin,[27] Wiseman,[33] and others[18] have described refractile unstained particles within the hazy cytoplasmic remnant surrounding the nucleus of the effete lymphocyte. These entities are either disintegration products of the dying cells or normal structures which have lost their staining characteristics and have been modified morphologically in the course of cellular change.[29] Hu[15] has verified this latter phenomenon in mitochondria following damage to the cells containing them. Shipley[25] expressed the opinion that the presence of these vacuole-like structures represented the index of degenerative change. Auer[1] demonstrated the presence of peculiar bodies within the cytoplasm of large mononuclear cells in a case of acute leukemia following massive hemorrhage. These bodies appeared black at a certain focus but were highly refractile. They occurred but rarely in the small lymphocyte and varied in shape from globules to rods. Bohrod[3] described solid, hyalin bodies in 18% of all the white blood cells in a case of acute myelosis. Comparatively few were in lymphocytes and they were not visible with the oil immersion lens. Doehle[34] indicated certain bodies present in the leukocytes of fixed smears taken from patients with scarlet fever. They have since been

described in other conditions.[2] These structures are not visible in the wet preparation and evidently take nuclear stains. Despite the multiplicity of these cytoplasmic inclusions, each has its own fairly well defined characteristics which preclude error in interpretation.

Description. The globular particles I wish to describe have evidently not been noted previously as constant features of white blood corpuscles. They occur almost exclusively within lymphocytes.* Very rarely have structures with somewhat similar characteristics been observed in monocytes. They have not been identified in any of the other blood elements. These bodies are small, smoothly contoured spherules varying in size from a point (oil immersion) to about 0.5 μ in diameter. The average has a diameter of 0.25 μ. In general however, they fall into two size groups; one in which the diameter ranges from a point to 0.25 μ, and the other from 0.25 to 0.5 μ. In a series of 50 protocols the predominance of the smaller form was in a proportion of 2 to 1.

These bodies have been noted almost entirely in wet preparations. Only 3 times in 30 fixed smears stained with Wright's stain has the presence of granules resembling them been demonstrated. Two of these preparations were drawn from a patient with hemochromatosis and one from a case of infectious mononucleosis. The blood for these smears was drawn concomitantly with that for wet preparations all of which contained a significant number of granules. Alcohol fixation and staining with the Romanowsky dyes evidently obscured this element.

The spherules are markedly refractile, appear solid black at one focus and have a colorless glassy sheen at another in the unstained state. Ordinarily a single granule and much less often 2 or 3 are present in one lymphocyte. In several cases of chronic myelogenous and lymphatic leukemia and one undiagnosed splenomegaly with anemia in an infant there have been observed as many as 8 in a single cell, but never more. Only 1 or 2 cells among 200 to 400 lymphocytes counted in each of these patients displayed this number. The characteristics of the globular particles were exactly the same as those in the ordinary lymphocyte. They were all approximately the same size (0.3 μ). When two granules were present in a single cell, as occurred in about 30 to 40% of the spherule containing lymphocytes, one was more often much smaller than the other.

These intracellular inclusions are actively motile. In preparations examined promptly after withdrawal, their motility is most striking. They course about usually within the perinuclear zone, often under or over the nucleus, in a zig-zag fashion. Occasionally

* Dr. William Dameshek writes us that he has personally examined these preparations and that "there is unmistakably a rather opaque refractile granule in many of the lymphocytes."—[EDITORS.]

they obtrude toward the periphery of the cell but generally they remain quite close to the nucleus. As they approach the nuclear *Hof* they frequently impinge upon other less motile cytoplasmic structures (mitochondria and segregation apparatus) lending to these

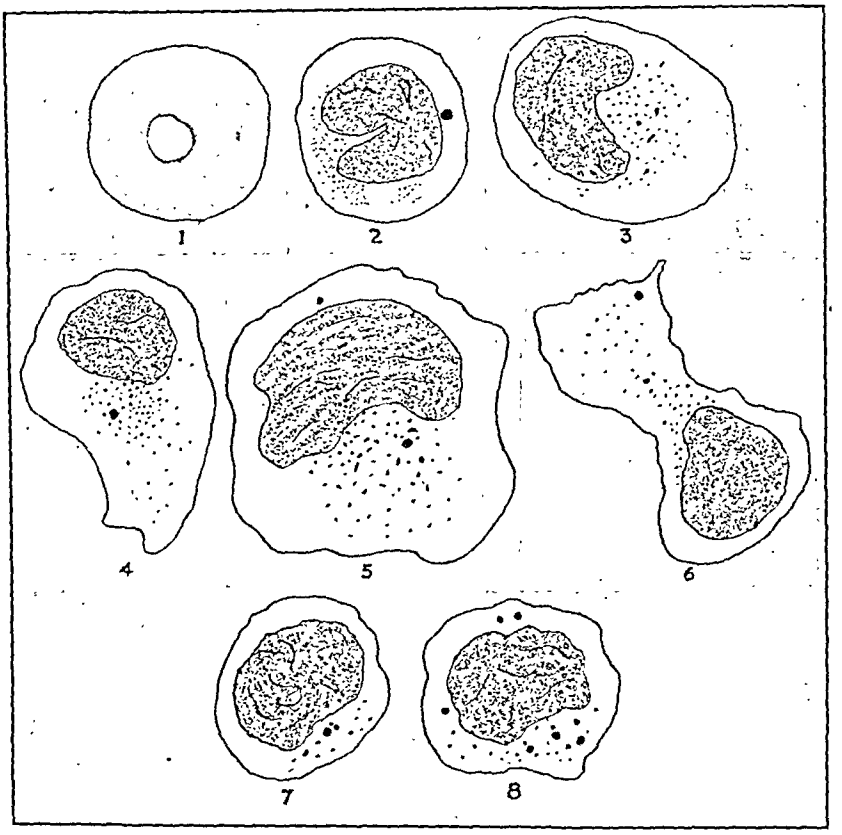


PLATE I.—All of these cells are unstained and are drawn from wet preparations of human blood. (1) This is a normal erythrocyte inserted for size contrast. (2) A small lymphocyte with a large refractile body opposite the indentation of the nucleus. The clumps of fine smudgy granules are probably mitochondria. (3) An intermediate lymphocyte with many fine and a few coarse, smudgy granules in the bay of the nucleus. There are no refractile bodies present. (4) A motile lymphocyte with a single, small refractile spherule which dragged along behind the nucleus. (5) A large lymphocyte containing three refractile bodies. Two of them are large and one is point-sized. (6) A rapidly motile lymphocyte with two refractile bodies, one of which remained close to the nucleus whereas the other bobbed about in the dragging tail of the cell. (7) A small lymphocyte in a preparation standing for 4 hours. The two refractile bodies, of unequal size, have come to lie together, close to the flattened portion of the nucleus. (8) A lymphocyte observed in the blood of an infant with anemia and splenomegaly. There are six refractile bodies present.

added impetus and receiving in return retardation and deflection of their momentum and course .[6,17] As has been noted, the motility of the other visible cytoplasmic elements was neither as rapid nor extensive as that of the refractile bodies.

The wandering spherule often ceased movement momentarily, vibrated in a rotatory fashion about a single point, and then resumed its course again. Frequently this pause was prolonged and even vibration ceased for as long as 30 minutes. Occasionally vibration returned intermittently without any other movement of the granule. Eventually the progressive motility usually returned. The impression garnered from continued observation was that the general course tended to be toward and away from the region of the centrosphere in the indentation of the nucleus. Ultimately, as the preparation aged or some toxic dye (Janus green, etc.)[4,11] was added to it, the refractile body came to lie at this central point in the nuclear bay and remained here constantly without visible motility or change until the cell disintegrated in 72 to 96 hours. At this time the granule, often indistinguishable from the products of cellular degradation, came to lie in the surrounding medium.

When two refractile granules were present in the same cell, the smaller one was usually found on the same side of the nucleus as its indentation and did not often migrate for any great distance from this point. Its movement was of the same type as that of the larger body in that it, too, had a zig-zag course as well as a vibratory character, the latter being the more frequently evident. The smaller granule also seemed to be controlled by some force exerted by the centrosphere for it appeared to jog about much like a rubber ball on an elastic band. Occasionally, the two bodies remained vibrating in a jerky fashion at opposite sides of the nucleus and then slid rapidly toward each other to meet in the nuclear bay without any evident jolt. Ultimately, as the preparation became older ($1\frac{1}{2}$ to 4 hours), the two came to lie proximate to each other in the vicinity of the centrosphere where they remained motionless. In this state they closely resembled the centrioles as illustrated by Cowdry[7] and Maximow[20,21] save for their unequal size.

The lymphocytes containing these bodies were themselves often actively motile when unstained or stained with neutral red alone. When the temperature of the warm box was raised to 39 or 40° C. the cells assumed their characteristic motility[10, 19, 23] and the granule was observed bobbing along passively in the streaming tail of cytoplasm. The spherule retained, however, its own relative motility for when the cell became static the refractive particle again resumed its own wanderings. Rarely the body was observed in the thin film of cytoplasm ahead of or underlying the moving nucleus but it rapidly slipped to the rear of the cell.

The refractile globules were not present in all lymphocytes. In a series of 120 wet preparations, both unstained and supravitally stained, viewed in a warm box at body temperature, they were present in an average of 34% of all lymphocytes. Fifty to 150 lymphocytes were counted in each specimen. The range extended

from 6 to 55%. In the great majority of these preparations the refractile granule bearing lymphocytes averaged 20 to 45% of the total lymphocytes counted. In a series of counts done upon 30 normal individuals an average of 39% of the lymphocytes contained one or two bodies. In 16 patients with some pathologic process which might conceivably influence the lymphopoietic system (tuberculosis, lymphatic leukemia, Hodgkin's disease),[10] 34% of the lymphocytes contained the granule. In a mixed series of patients suffering from all types of disease (rheumatic fever, pneumonia, diabetes mellitus, heart failure, trichinosis, etc.) the percentage of lymphocytes bearing the body closely approximated the mean of all the cases examined (36%). Only in infectious mononucleosis (1 case) was the percentage observed to remain persistently low (6 to 13%). In 10 individuals upon whom counts were done on 4 successive days the proportion of granule bearing cells was noted to remain remarkably constant in each person from day to day. The deviation was no more than 2 to 5%.

The globules were present more often in the small lymphocytes than in the large and intermediate forms.[8,9] They were more common in the mature and older lymphocytes whereas the young and immature forms contained them infrequently. The criteria of Hu and Wiseman[15,32,33] were utilized in the estimation of the age of the cells. Plasma cells contained the bodies in less than 3% of those identified. In the effete lymphocytes it is often impossible to distinguish the bodies from the products of disintegration present.

When observed with the polarizing microscope the granules were not doubly refractile. In preparations treated with 0.5% acetic acid they became darker, retained their form and contour, but lost much of their refractibility. They were entirely obscured by methyl and ethyl alcohol, and could not be recognized when the smear had been fixed by drying. In the wet preparation they were unchanged in appearance when subjected to temperatures ranging from 15° to 45° C. Motility was retarded with lowering of the temperature. Neutral red[11] imparted to them a dark mahogany hue but they did not appear to be stained by methylene blue, eosin, azure, Sudan III, osmic acid, Janus green, Bismarck brown, or iodin. Owing to the refractibility of the particles it was almost impossible to determine conclusively whether or not they were stained in any slight degree by these substances.

Comment. The significance of these refractile globules is not recognized. It is possible that they are products of cellular disintegration. Their predominance in the older lymphocyte suggests this to a certain extent. Their presence in the actively motile lymphocyte is somewhat unfavorable to this point of view, particularly since the continued activity and failure of the nucleus to become stained with neutral red is significant of the cell's viabil-

ity.[27] Furthermore, the globules are present in no greater proportion of the cells in the long standing (2 to 4 hours) than in the fresh preparations; nor is there any perceptible decrease in their numbers after 24 hours. On the other hand, with prolonged contact with a somewhat concentrated solution of neutral red, the lymphocyte will be damaged, motility will cease, and the nucleus will begin to take the stain.[4,27] At this time the movement of the refractile body will rapidly subside even though Brownian movement is initiated in other cytoplasmic particles. Likewise, the application of Janus green, which is rather toxic to intracellular activity,[30] produces rapid cessation of the granular motility and stasis within the *Hof* of the nucleus even before the mitochondria are fully stained. In view of these facts, therefore, it is readily conceivable that the globule is a natural component of the extra-nuclear substance of the lymphocyte and as such responds in a parallel fashion to external stimuli.

The failure of the particle to be stained by either osmic acid or Sudan III and its inability to exhibit doubly refractile qualities are points unfavorable to the belief that it is lipoid in nature.

As has been stated, the appearance of the granules after they have become static in the center of the nuclear indentation is very similar to that described by many as the centriolar apparatus.[7,20,21] The presence of one, three, or more of these in a mature, non-dividing, mononuclear cell rather disproves this possibility. In cells observed dividing amitotically in the wet blood spread, the globule remained passively wherever it happened to lie and exhibited little disturbance as the result of separation. One daughter cell contained the body, the other did not. That the granule is strongly influenced by centrosomal activity, however, cannot be disputed, since its movement apparently centers about this structure and it ultimately comes to lie in its immediate vicinity.

Failure to distinguish the refractile spherules from the other previously noted structures within the normal lymphocyte is remote. Lawrence and Todd[16] have described the appearance of the neutral red staining bodies as "refractile blackish red." These, however, usually number 2 to 25 per cell and their red glint when stained makes them sufficiently distinctive to one familiar with the supravital technique.[8,9,27] Sabin has noted, further, that their index of refraction is similar to that of the cytoplasm and they are observed therefore with difficulty in the unstained state.[26] Prigosen has described the presence of neutral red staining bodies which he claimed might not take the dye immediately.[25] His illustrations lend no weight to the possibility that they are similar to the globule I have demonstrated. He enumerated four cytoplasmic granules of the lymphocyte, only one of which was not stained by neutral red or Janus green and this was a lipoid droplet. Mitochondria,

by reason of their smudgy, non-refractile character, their number, size, rod shape, and specificity for Janus green may not readily be mistaken for the refractile body.[5,8,9] Wiseman has noted the presence, occasionally, of non-staining refractile granules which have been found, however, only in those cells which do not contain mitochondria.[29,32,33] Furthermore, he has demonstrated as many as 30 in a single large lymphocyte. Finally, the azure granule of Wolff and Michaelis[4,27] is not visible in the unstained state and is probably not stained by the supravital dyes.

In only 3 cases of 130 examined was there any marked deviation from the average percentage of granule bearing lymphocytes observed. As has been previously noted in 8 counts done upon a patient with infectious mononucleosis wherein 57 to 130 lymphocytes were counted in each preparation only 6 to 13% of them contained the refractile body. The absolute number of lymphocytes containing these bodies was also reduced although not to as great a degree. In 5 counts done upon 2 patients with myelogenous leukemia in each of which 200 to 400 leukocytes were counted, only 2 to 9 lymphocytes were observed. Of these, 0 to 50% contained refractile bodies. In these cases, however, the absolute number of such lymphocytes was not always reduced since the total leukocyte count varied from 200,000 to 500,000 per c.mm.

In a series of 12 individuals upon whom serial counts were done for 72 hours following intracutaneous injection of tuberculin no significant change in the percentage of granule bearing lymphocytes was noted regardless of the extent of the local or systemic reaction.

Summary and Conclusion. Description is given of the presence of a motile, refractile globule which is normally present in a fairly constant percentage of the lymphocytes of peripheral blood observed in wet preparations. The bodies vary in size from a point to about 0.5 μ in diameter and appear in approximately 34% of the circulating lymphocytes. They occur for the most part in normal lymphocytes but have been noted in pathologic cells as well. The numbers of granule bearing lymphocytes remain quite constant in the same individual from day to day. They do not appear spontaneously or disappear in the standing blood spread. One or two are observed in a cell, rarely more. The spherule is neither mitochondrial nor one of the neutral red staining bodies previously described as existing in lymphocytes. It is probably neither of a lipoid nature nor a portion of the centrosphere. It appears to be a hitherto undescribed constituent of the cytoplasm of the lymphocyte.

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BARTONELLA CANIS INFECTION IN RELATION TO SECONDARY ANEMIA AND THE ASSOCIATED UNDERLYING LESIONS.

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In 1928, Kikuth[1] described an organism associated with a peculiar progressive cyclical anemia in splenectomized dogs. Close similarity to the Bartonella group, as regards biologic and morphologic characteristics together with the almost identical associated blood dyscrasia, induced him to designate this organism as Bartonella

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canis. "These organisms," he says in his original report, "remind one partly of the Bartonella bacilliformis (human) and partly of the Bartonella muris." He believed them to be causative of the accompanying anemia, acting in the capacity of a parasite in the dog's red corpuscles, in or on which they were found. With Giemsa's stain these parasites showed up well resembling either cocci or bacilli. Their morphology was not, however, constant, being changeable into manifold shapes and occupying varying positions in relation to each other.

Splenectomized dogs sicken regularly if infected with Bartonella, the infection assuming either an acute or a chronic course. Death has occasionally been observed at the height of the acute infection, but recovery is the usual outcome in the chronic type. Normal non-splenectomized dogs, if injected with Bartonella, develop an abortive illness, passing-off into a latent infection, which may occasionally be activated by splenectomy. Kikuth failed in numerous attempts to grow the organism on various types of culture media. He mentions therapeutic doses of neosalvarsan as having excellent curative action.

In 1909, Barton[2] had suggested that the bacilliform bodies, found in the blood of human beings suffering from Peruvian Oroya fever, were causative of that disease. Strong[3] and his associates, in their report of the first expedition to South America, speak of them as protozoa and suggested the term "Bartonella." Noguchi,[4] in studying a fatal case of Oroya fever, had the fortune to isolate the parasite in pure culture and with the same culture produce characteristic disease symptoms in animals. In further experiments Noguchi[4] found similar Bartonella-like bodies in the blood of a splenectomized rat. Lauda[5] gives us a detailed account of the anemia in splenectomized rats, in which bodies occurred in the erythrocytes strikingly similar to those seen by Noguchi.

Regendanz and Reichenow,[6] following up the work of Kikuth, give us a rather careful and detailed descriptive picture of this polymorphous parasite. They regard the differentiation into rod-like and cocci forms as not particularly well chosen because the rods are for the most part found to consist of beaded little bodies (cocci); naturally, therefore, not individual entities but rather chains of parasites. In their opinion the basic form of Bartonella canis is the coccus form and all complicated formations occurring in the red corpuscles are simply colony growths.

Within the past year various papers have appeared in which the nature and course of the anemia associated with Bartonella bodies have been recorded by American workers, notably Knutti and Hawkins,[7] Rhoads and Miller.[8] Knutti and Hawkins,[7] working with splenectomized bile fistula dogs, noted periods of bile pigment overproduction and anemia occurring spontaneously in conjunction

with the presence of Bartonella bodies in the blood. Prior to these observations Queen, Hawkins and Whipple,[9] also working with splenectomized bile fistula dogs, were well acquainted with the cyclical bile pigment overproduction, anemia and intoxication arising in these dogs. They even went as far as to determine the daily quantitative overproduction of bile pigment during these cyclical periods, which in some instances reached 8 to 10 times control values. Thus in one cycle of pigment overproduction an average 24-hour output of 581 mg. of bile pigment was recorded. On one day during this cycle an output of 878 mg. of bile pigment was observed, or more than ten times the control level (78 mg. per day). They had been at a loss to satisfactorily explain these phenomena and failed to recognize Bartonella bodies in the blood at that time, presumably no search having been made. Thus in the absence of a demonstrable infection, it had been assumed that the periods of bile pigment surplus and anemia were of physiologic origin, related to a lack of spleen and bile constituents. With the finding of the Bartonella canis in these blood dyscrasias, the situation seemed to clarify and the evidence pointed to that organism as the probable etiologic factor.

Various investigators have observed periods of anemia in splenectomized dogs. Krumbhaar[10] looks upon the temporary anemia as a physiologic response to the loss of the spleen. He believes that the normal spleen in addition to its hemolytic function has also a stimulating effect on the red blood-cell formation, citing as supporting evidence the fact that anemia follows its removal. He regards this anemia as due to a loss with the spleen of a property which aids erythrocytes formation, such as conservation of the iron of broken-down red corpuscles. This function is in time taken over, at least in large part, by other members of the reticuloendothelial system, accounting for the temporary character of the postsplenectomy anemia. Furthermore, normal spleen extract has a stimulating, not an inhibitory, action on erythropoiesis in the bone marrow.

The question now arises, in the light of our more recent knowledge, whether this temporary postsplenectomy anemia observed in the past could possibly have been the result of an unrecognized latent Bartonella infection, activated by splenectomy. Against this likelihood stands an array of convincing evidence. The majority of investigators are in agreement, that spontaneous latent infection with Bartonella canis does not become activated in normal dogs with splenectomy alone. A few workers, however, cite such to be the case in an occasional simple splenectomized dog. I have, in the course of my experiments, observed 2 dogs for 60 days following simple splenectomy, during which time there was no evidence of Bartonella infection or Bartonella bodies in the blood, yet an anemia developed similar in character and degree to that described by

Krumbhaar[10] and others[11] as postsplenectomy anemia. A transient, non-infectious, postsplenectomy anemia, therefore, seems to be the most likely explanation.

TABLE 1.—CHANGES IN THE ERYTHROCYTE COUNT AND HEMOGLOBIN CONTENT OCCURRING IN DOGS WITHOUT BARTONELLA INFECTION AFTER SIMPLE SPLENECTOMY, OBSERVED FOR A PERIOD OF 60 DAYS.

Dog. 269.			Dog. 312.		
After splenectomy, time in days.	R. B. C.	Hemoglobin.	After splenectomy, time in days.	R. B. C.	Hemoglobin.
*	5.81	94	*	6.10	80
3	5.20	84	3	5.80	70
5	4.90	80	5	5.75	75
8	5.40	80	8	5.50	68
12	5.20	78	12	5.50	60
18	5.20	84	18	5.00	58
24	5.00	75	24	5.00	55
30	4.80	67	30	4.90	55
31	**4.80**	**63**	36	**3.30**	**46**
42	5.00	67	42	3.90	46
48	4.85	61	48	4.00	48
54	4.90	77	54	4.40	52
60	5.00	84	60	4.60	55

* Preliminary count and estimation.

In both of these dogs a secondary anemia gradually developed following the operation. The anemia in both cases was most severe during the fifth week. Then with a gradual improvement, the blood picture tended to approach the pre-operative level. As may be readily seen from the table, the latter had not been attained in either dog at the end of the 60-day period of observation. Krumbhaar[10] regards the average length of time for complete restoration of the blood picture to normal as 3 to 4 months. The hemoglobin decrease occurs somewhat sooner and is also more outstanding than the red cell drop, and as improvement occurs the increase in hemoglobin tends to lag notably behind the erythrocyte increase.

Either splenectomized bile fistula dogs (Knutti and Hawkins[7]), or simple splenectomized dogs, fed on deficiency diets producing black tongue (Rhoads and Miller[8]), appear to show regular spontaneous involvement with Bartonella canis and anemia. The authors are insistent that in both experiments simple splenectomy will not bring about Bartonella infection. Krumbhaar,[10] in his extensive studies of changes produced in the blood by splenectomy, failed to note a marked degree of anemia or the presence of Bartonella bodies, even though the spreads have recently been reëxamined with this point in view. Being acquainted with the infectious anemia (Bartonella) lit up by splenectomy in rats and reported by Lauda,[12] he was especially on the lookout for these parasites. It may be said that simple postsplenectomy anemia does not attain the severity of that observed complicated by Bartonella infection. Furthermore, the isolated simple splenectomy cases reported in

earlier medical literature as developing typical Bartonella canis-like anemia, may in all probability be related to some such diet deficiency complication referred to above.

Method. The work was begun by transmitting the Bartonella infection to a simple splenectomized dog by the injection of 5 cc. of Bartonella blood obtained through the kindness of Dr. G. H. Whipple, to whom I am also indebted for valuable suggestions in pursuing the problem. The 5 dogs on which this study was based were infected from this dog as the original source. One dog (No. 269) was used as a special control, in addition to the earlier simple splenectomies done in this department. Blood smears were taken at almost daily intervals and examined for the organism, using the Giemsa method of staining. Frequent red cell counts and hemoglobin determinations were made at weekly or lesser periods. The more frequent blood examinations were made at those periodic intervals in the course of the infection when the blood smears became positive for the Bartonella bodies. By this method, sudden transitions in the blood could be more easily detected and the relationship of the appearance of the organism to the developing anemia better evaluated.

Infection Cycle of Dogs With Bartonella Infection. In general, the course of the infection developing in our dogs, excluding minor variations, corresponded rather closely to that reported by other earlier investigators, notably Regendanz and Reichenow.[6] The incubation period after injection varied from 7 to as much as 15 days, a somewhat longer period than that usually reported (3 to 5 days). This period was followed by the appearance in the blood stream of the Bartonella organism at first few in number, then increasing rapidly for several days only to decrease and disappear suddenly. An interval of freedom from the organism, variable in the different dogs from several days to a week or more, but present in all, occurred before recurrence with rapid proliferation was again observed in the blood smears. As regards the general duration of the subsequent intervals and the renewed attacks which followed periodically, one upon another, it may be said that it varied throughout the course of the infection. The shortest intervals and the longest attacks took place at the time that the infection course seemed to be at its peak, as judged by the number of organisms present and the marked blood destruction with its attendant severe anemia. By attack, one refers to that time interval during which the organisms were numerously present in the red corpuscles and detectable by the microscope.

Thus Dog 24 (Fig. 2) showed a rather regular course at first, for a long time running attacks of 8 to 10 days' duration with intervals averaging 10 days. After the fourth attack, which was preceded by a shorter interval of 4 days, an irregular course developed until the attacks ceased altogether. A different course was observed in Dog 25 (Fig. 3), in which at the beginning long lasting intervals occurred, which were separated only by short attacks, and later two long attacks of 10 days' duration were followed by an attack

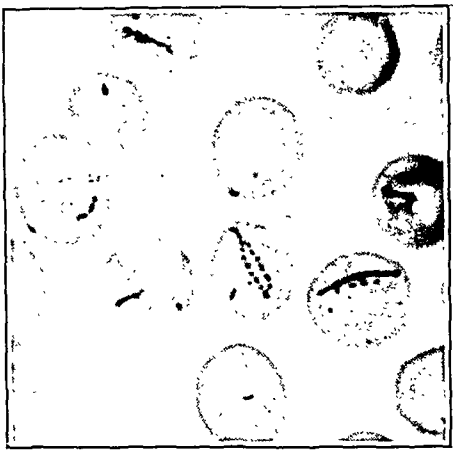


FIG. 1.—Blood smear obtained from Dog 24 at the peak of anemia. Various forms of Bartonella bodies are clearly demonstrated, *viz.*, single spherical forms, long beaded rodlike forms, simple rod forms and complicated formations. Giemsa stain. × 1600.

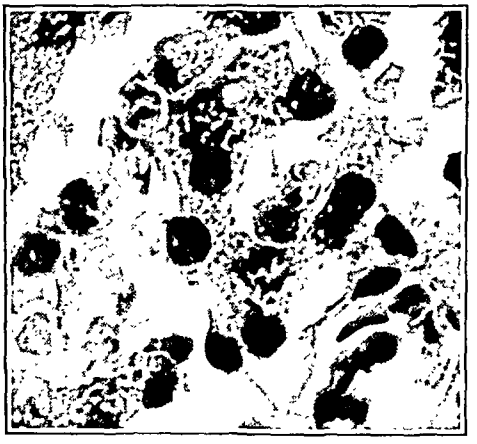


FIG. 7.—Photomicrograph of liver from Dog 25. Numerous Kupffer cells are present. These appear for the most part swollen and block the lumen of the intralobular capillaries. × 1050.



FIG. 8.—Photomicrograph of bone marrow from Dog 25. This section was taken from the proximal end of the femur. There is a marked hyperplasia of all the elements of the bone marrow. Azure II eosin stain. × 436.

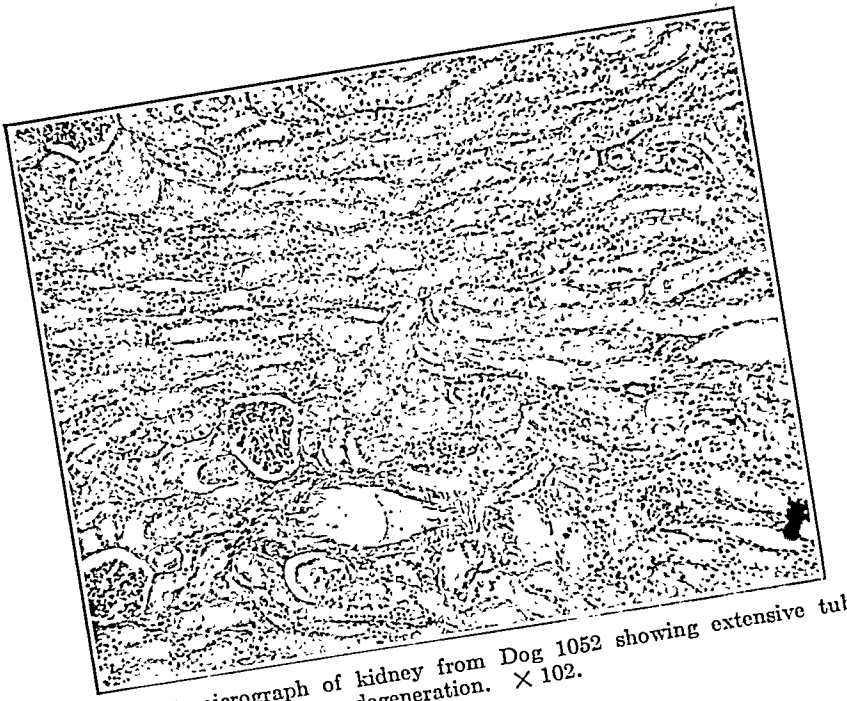


FIG. 9.—Photomicrograph of kidney from Dog 1052 showing extensive tubular degeneration. × 102.

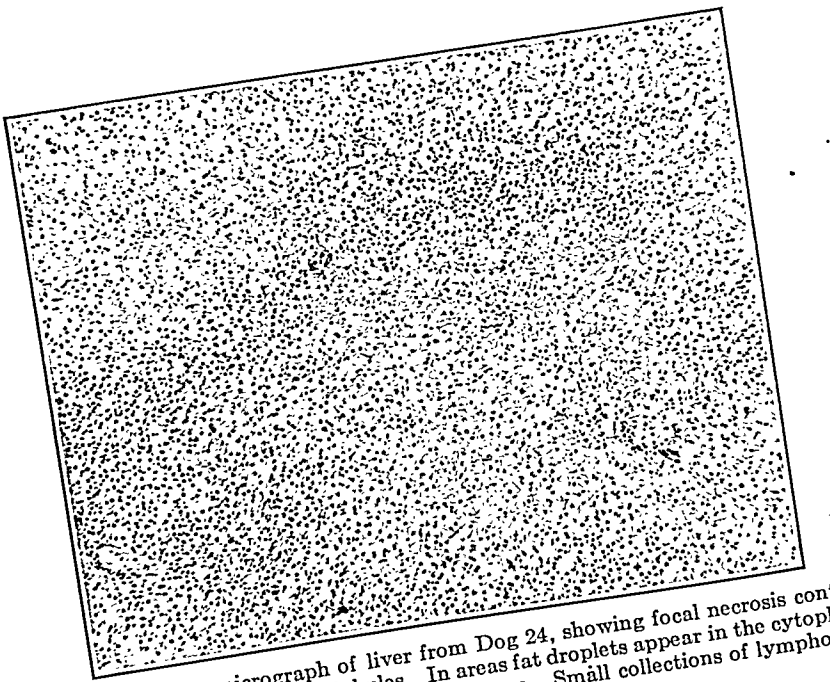


FIG. 10.—Photomicrograph of liver from Dog 24, showing focal necrosis confined principally to the center of the lobules. In areas fat droplets appear in the cytoplasm. Kupffer cells are small and normal in appearance. Small collections of lymphocytes are encountered in the periportal areas. × 102.

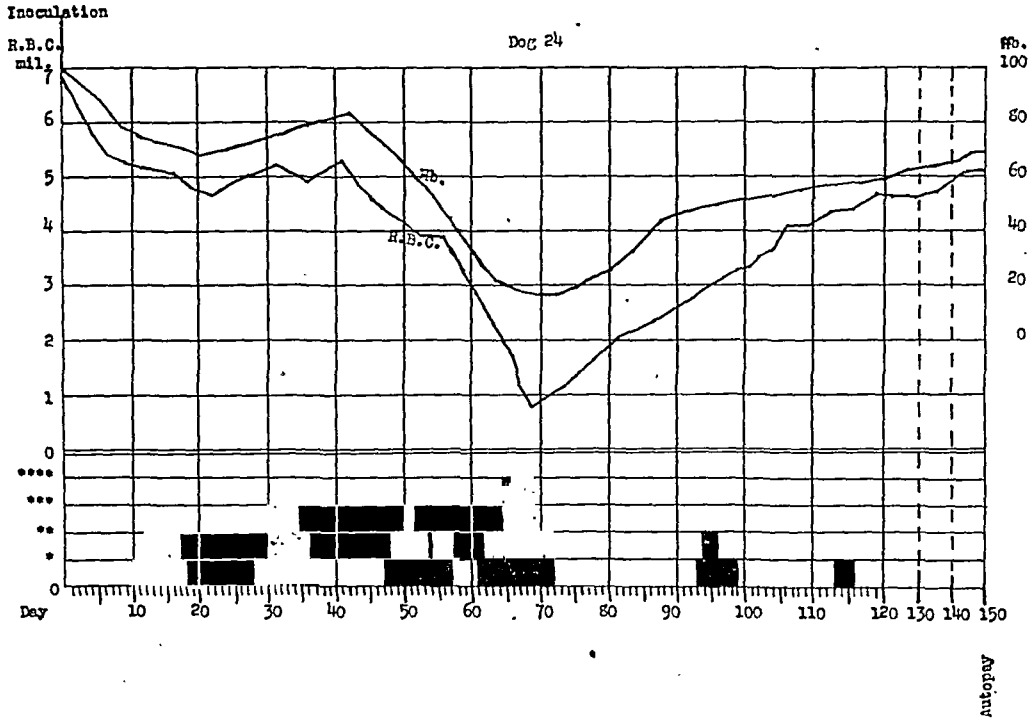


FIG. 2.—Dog 24. Bartonella incidence and anemia in injected splenectomized dogs. **** Preponderance of blood cells containing Bartonella. *** Several red cells with Bartonella per field (oil immersion). ** Average one organism per field (oil immersion). * Occasional organism in smear.

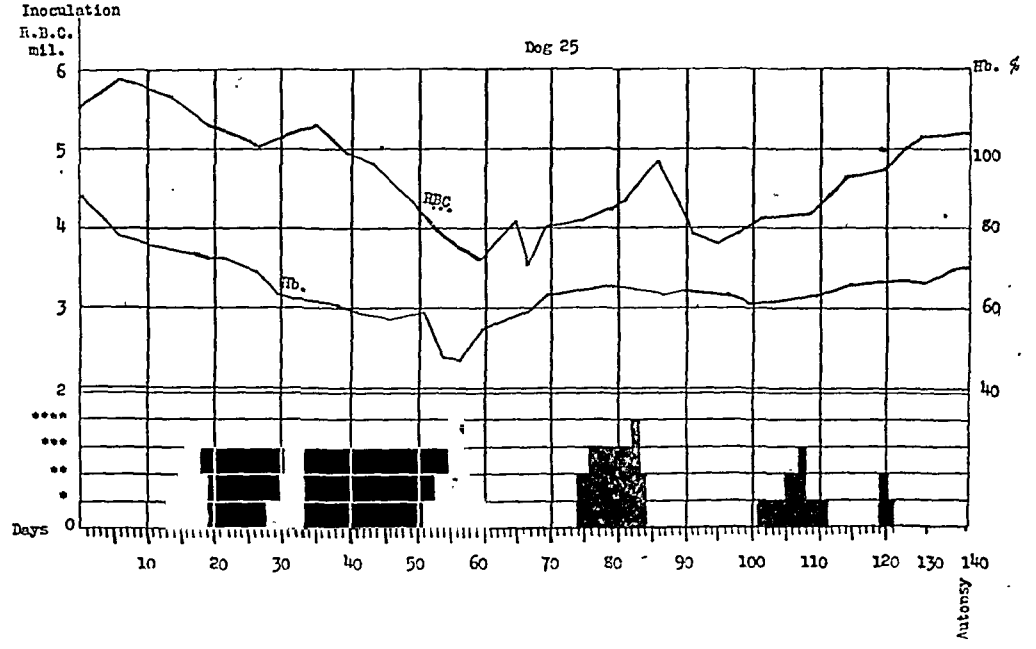


FIG. 3.—Dog 25. Bartonella incidence and anemia in injected splenectomized dogs. ****Preponderance of blood cells containing Bartonella. *** Several red cells with Bartonella per field (oil immersion). ** Average one organism per field (oil immersion). * Occasional organism in smear.

of 2 days, terminating the course of the infection. In Dog 268 (Fig. 4) the following course occurred: After two short-lived attacks lasting 5 days and separated by an interval of 7 days, there followed a 14-day interval. The new attack lasted 18 days, whereupon an 11-day interval occurred. Then followed one attack of 3 days after which the smears remained negative. In this dog the blood picture failed to return to a normal level 2 months after the last organisms appeared. In all other dogs after the infection sub-

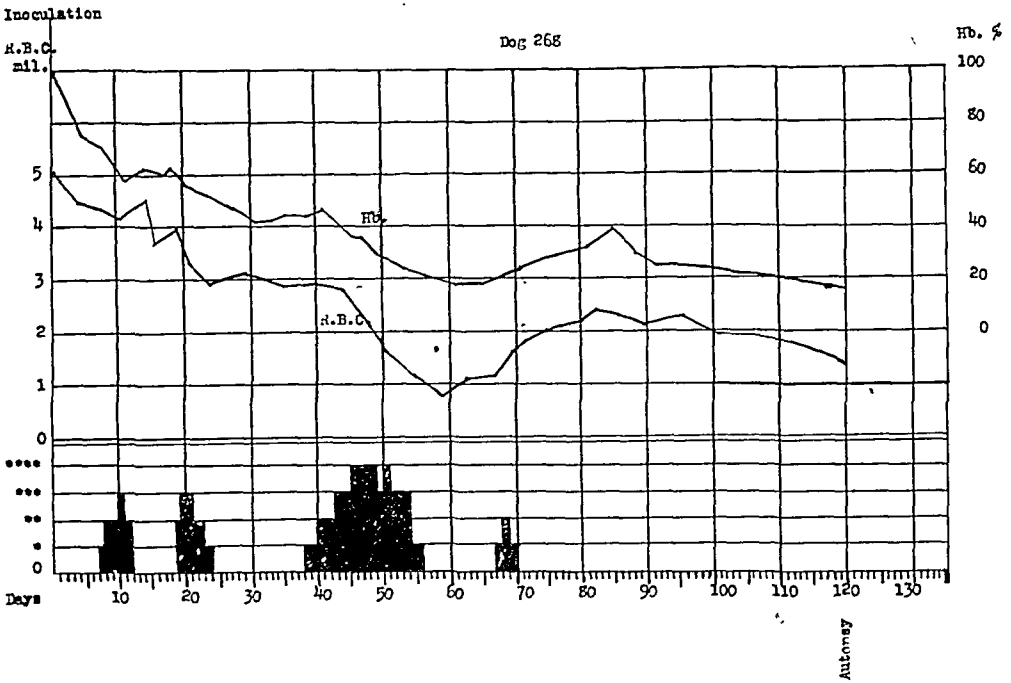


FIG. 4.—Dog 268. Bartonella incidence and anemia in injected splenectomized dogs. ****Preponderance of blood cells containing Bartonella. *** Several red cells with Bartonella per field (oil immersion). **Average one organism per field (oil immersion). * Occasional organism in smear.

sided, the blood reached or tended toward normal levels. One is inclined to believe that an abdominal wall sinus in Dog 268 draining at intervals throughout the latter part of the Bartonella and post-Bartonella infection period accounted for the severe persistent anemic blood picture. Interesting was the course of Dog 312 (Fig. 5) in that only two attacks occurred. The organisms appeared first in the smears, 7 days after injection with Bartonella positive blood and again after an interval of 9 days. Both attacks lasted 5 days and in neither instance were the organisms very numerous. The infection course of Dog 1052 (Fig. 6) was cut short by sacrificing the animal in the early stage of the infection, 10 days after the first appearance of the Bartonella and while the blood smears were

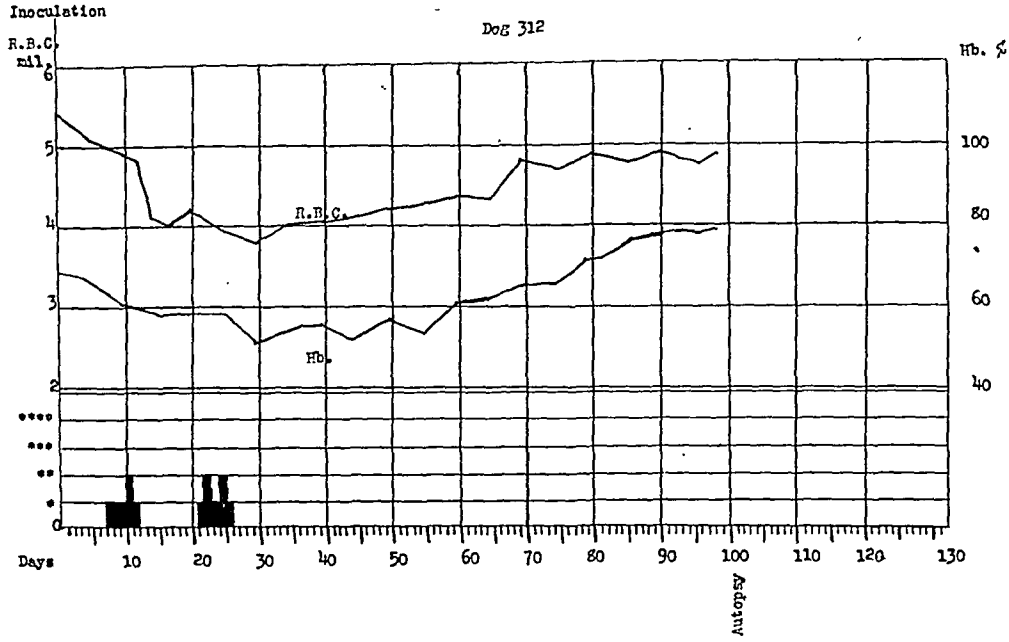


FIG. 5.—Dog 312. Bartonella incidence and anemia in injected splenectomized dogs. ****Preponderance of blood cells containing Bartonella. *** Several red cells with Bartonella per field (oil immersion). ** Average one organism per field (oil immersion). * Occasional organism in smear.

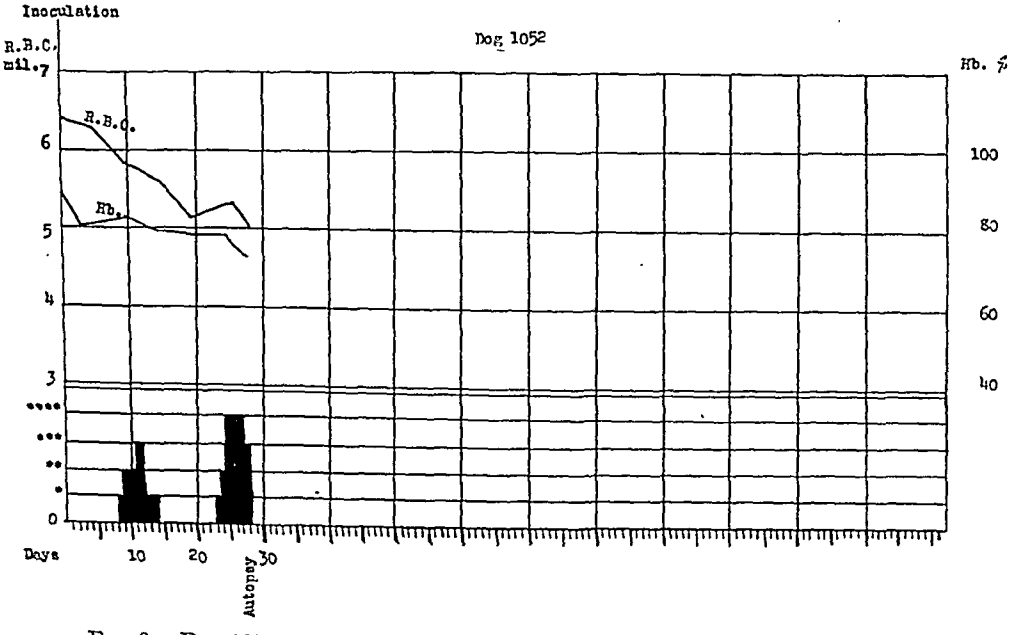


FIG. 6.—Dog 1052. Bartonella incidence and anemia in injected splenectomized dogs.

showing organisms in great numbers. This procedure was adopted in order to determine and study the histologic changes occurring in the early stage of the Bartonella infection. Blood regeneration, as judged by the numerous immature forms (macroblasts, normoblasts) and the high reticulocyte count in the smears, was fairly active.

Effects of Bartonella Canis on the Organism. The outstanding feature of the Bartonella infection, observed in the dogs as a group, was the severe type of anemia encountered and associated with an extreme degree of general emaciation and physical weakness. It has been said,[6] that Bartonella canis anemia is of lesser intensity than the infection in man with Bartonella bacilliformis (Oroya fever) and the infection in the splenectomized rat with Bartonella muris. One is rather reluctant, however, to fully subscribe to this statement, for 2 of our dogs (Nos. 24 and 268) developed at the height of their infection an anemia of extreme severity in which the red corpuscles dropped to 910,000 and 750,000 per c.mm. respectively. The hemoglobin determination in both dogs read less than 3 gm. per 100 cc. At the time the above blood findings were recorded, these dogs showed extreme body emaciation and such physical weakness that the exertion of a slow walk over a short distance gave way to a faltering gait and the development of severe dyspnea. In Dog 268 life was despaired of. Evidence of blood regeneration, however, went hand in hand with blood destruction and one was immediately struck by the large number of immature polychromatic and nucleated red cells occurring simultaneously with the degenerated forms. The reticulocyte count was noted as high as 30%, and undoubtedly reached higher levels in some cases. This condition existed not only at the height of the infection and after development of a profound anemia, but shortly after the first appearance of the organism in the blood smears, immature erythrocytes sprang into evidence. During the peak of the infection organisms appeared almost continuously in the blood stream, without interruption by a Bartonella free interval. Finally, after the infection began to wane, the blood (except in Dog 268) rapidly approached normal levels. The color index was in general below 1. Our animals recovered immediately as soon as the course of the infection changed for the better, namely when instead of long lasting attacks, intervals of longer duration appeared. No fatality occurred in our dogs. Also in subsequent attacks of long duration, there developed in these dogs decrease of hemoglobin and red cell count, which rose again during the interval when the Bartonella were not able to be found microscopically.

Autopsy Reports. All dogs used in these experiments had autopsies performed. Because of the loss of the spleen, which in mammals contains the bulk of the reticuloendothelial system, and influenced by the concept of reticuloendothelial organ interdependence, the histology of the lymph nodes, bone marrow, liver, lungs and kidneys were chiefly studied. The

dogs were killed with an overdose of chloroform and immediately sectioned. It might be mentioned that in all cases search was made for accessory spleens, but none were found. One dog (No. 1052) was autopsied at an early period of infection; another (No. 25) late in the infection period, while the remaining dogs (Nos. 24, 268, 312) were sectioned at various intervals after the last appearance of organisms in the blood smears. One splenectomized dog (No. 269) was used as a control and autopsied 160 days after splenectomy. A routine Zenker formol fixation, paraffin embedding and hemotoxylin and eosin stains was used. In the case of the lymph nodes and bone marrow special staining with eosin azure II was employed. Detailed protocols have been omitted.

Dog 1052. Autopsy in the early stage of the infection; 21 days after the first appearance of the organism and while the blood smears were showing the Bartonella bodies in great numbers. The dog was beginning to show emaciation and physical weakness with marked wasting of the subcutaneous fat. A light bile discoloration marked the wasted fat. The blood was thin and watery. The lungs were collapsed, the anterior surfaces being pale and the posterior areas more of a dark red color. No areas of consolidation were encountered. On section a mild degree of edema was noted. Bronchial lymph nodes were only slightly enlarged. The heart was dilated and the myocardium pale.

The former bed of the spleen was represented by a mass of fibrous adhesions. The liver was of normal size, soft, and light brownish yellow. The lobular markings were not clearly distinguishable. Scattered widely through the liver were seen focal areas of necrosis. Both kidneys were of normal size. On section the cut surfaces appeared pale and mild degenerative changes were seen in the cortex and medulla. The individual structures outlined dimly and the cut surfaces appeared swollen. Adrenals were soft but otherwise of normal appearance. Mesentery and retroperitoneal lymph nodes were slightly enlarged, soft and swollen. Bone marrow of ribs, sternum and proximal ends of the femur and humerus was red and gelatinous. For histologic study see next section.

Dog 25. Autopsy late in the infectious period several days after the last appearance of organisms in the smears and 144 days after injection with positive Bartonella blood. The dog was in a moderately well-nourished condition, having shown a marked improvement in physical strength from that seen earlier in the course of the infection.

Both lungs and pleural cavities and the heart appeared to be normal. Paratracheal and bronchial lymph nodes were slightly enlarged and darky pigmented. The liver was dark brown, firm, with the external surfaces smooth, and the cut surfaces showing the lobules distinctly. The kidneys were pale, somewhat swollen and only faint focal suggestive areas of necrosis could be distinguished. Mesentery nodes in the upper abdomen were greatly enlarged. In the region of the celiac plexus these nodes formed a fused chained mass about 8 cm. in length. Isolated large nodes were also found. On section the nodes were soft, moist and of a pale fleshy color. Adrenal appeared normal. Bone marrow selected from the proximal ends of the humerus and femur was typically red and of a firm gelatinous character.

Dog 268. Autopsy on the 119th day after inoculation. This dog was in a weakened condition and failed to show improvement from a severe grade of anemia, in spite of the fact that organisms were not found in the blood on careful search during the 48 days prior to death. This persistent anemia was most probably associated with an abdominal wall sinus, draining intermittently during the last 10 weeks preceding the autopsy, due to persistent silk ligatures in the bed of the spleen. Organization of the granulation tissue was well advanced, and only small localized abscesses imme-

diately surrounding the silk ligatures were seen. Although the blood picture failed to improve, a marked gain in weight had been recorded since the terminal Bartonella attack.

Both pleural cavities and lungs were apparently normal. Bronchial and tracheal lymph nodes were slightly enlarged, firm and spotted with bluish-black pigment. The myocardium was pale. The liver was spotted with small grayish spots varying in size from that of a pin-head to that of a small pea. This was especially noted in the right lobe. Sections showed the same findings. Parenchyma appeared otherwise normal. Adrenals and kidneys were normal. Lymph nodes of the mesentery, especially of the duodenum and upper end of the ileum, were enlarged and tended to form fused masses. On section these nodes were soft and of a dull pink-grayish color. Bone marrow of the upper half of the humerus and femur was red, soft and jelly-like.

Dog 312. Autopsy 98 days after first injection. The animal was emaciated but for the past week a decided change for the better was observed as regards physical strength and weight gain.

The lungs were apparently normal. Bronchial and tracheal lymph nodes were palpably enlarged and of a firm flesh-like consistency. On section the cut surfaces were rather soft, moist and of a dull grayish-pink coloration. Heart was enlarged. The myocardium of the left ventricle was firm, the right flabby and dilated. Liver was slightly enlarged, firm in consistency, the external surfaces were smooth and the edges sharp. On section gray specks were noted scattered throughout the liver, but nothing further of a pathologic nature presented itself. Both kidneys were apparently normal. Retroperitoneal lymph nodes were variously enlarged some to the size of a small bean. On section these nodes showed a soft, moist pulpy parenchyma of yellow-pinkish coloration. Bone marrow taken from the upper humerus and femur was predominantly red, soft and gelatinous. Bone marrow of the sternum was also of the red type but rather scanty in amount.

Dog 24. Autopsy 90 days after the last appearance of the organisms in the blood smears. The dog was in an excellent physical condition and had completely recovered from the severe anemia and weakness present at the height of the infection. The lungs were apparently healthy throughout. The bronchial nodes were moderately enlarged and pigmented. The heart muscle was firm and of good tone. The liver, gall bladder and biliary tract, gastro-intestinal tract, adrenals and kidneys presented nothing abnormal.

Only a few fibrous adhesions marked the splenic bed. Mesentery lymph nodes, especially those confined to the upper abdomen, were enlarged and fused into long masses often approximating 6 cm. in length and 2 cm. in width. The individual nodes, although massed together, tended to remain discrete.

Bone marrow removed from the proximal ends of the humerus and femur was light pink, with scattered yellow areas of fat interspersed. The typical red variety of the dogs autopsied during the infective period was not in evidence.

Dog 269. Autopsy 160 days after simple splenectomy. The dog was not infected with Bartonella and was used as a control. We were especially anxious to observe both the macroscopic and microscopic changes which might occur with the loss of the spleen. Special search was made in the lymph nodes and other reticuloendothelial structures to determine whether demonstrable definite compensatory changes appeared. This dog had been injected with trypan blue a year previously, evidence of which could be plainly seen in the various tissues.

The lungs and heart were normal. Bronchial lymph nodes were only slightly enlarged, discrete and spotted heavily with a bluish-black pigment.

In the abdomen the omentum was the seat of marked bluish-black pigment deposit as were also the intestinal mesentery and to a minor degree the bowel wall. The liver was smooth, normal in size, firm and dark bluish-red. The same dark color prevailed on section. Gall bladder and ducts were normal. At the site of the splenic bed a smooth scar was found. No supernumerary spleens were found. The lymph nodes were only slightly enlarged and peppered with bluish black pigment deposits.

The adrenals and kidneys were normal in size; the surfaces, both external and cut, showing a faint bluish tinge against a dark red background.

Bone marrow removed from the proximal ends of the humerus and femur was a combination of the red and fatty varieties. The consistency was soft, pulpy in character and of a dull pink gray.

Histologic Examinations. In reporting on the histologic changes observed, the material examined is conveniently arranged in two groups: I. Tissues obtained during the active infection period or the acute anemia stage (Dogs 1052, 25, 268), and II, those from dogs autopsied some time after the infection had run its course (Dogs 312 and 24). Dog 268 is considered in Group I because, even though organisms were not detected in the blood for a long time, the animal had not recovered from the severe anemia.

Variations in individual dogs distinct from the group as a whole will be referred to specifically. Dog 269 (control) will be considered separately.

GROUP I. *Active Infection Period.* Microscopically, the liver cells show some granular and fatty degeneration, especially in the central portion of the lobules. The ordinary undifferentiated endothelial lining cells of the liver sinusoids are not affected. The Kupffer cells are present in great numbers and show marked phagocytic activity. They are for the most part enormously swollen and seem to block the lumen of the intralobular capillaries (Fig. 7). In some areas the Kupffer cells show such proliferation that accumulations encroach upon and compress the cords of liver cells. The phagocytic activity of the Kupffer cells can be readily judged from the granules of green waste pigment, engulfed erythrocytes in various stages of disintegration and hemosiderin granules in their protoplasm. The microscopic section suggests that large amounts of cellular débris circulate in the blood during the height of the infection, a factor undoubtedly accounting for the marked stimulation of phagocytic activity.

The liver cells from Dog 25 do not show the marked degree of degeneration seen in Dogs 1052 and 268. The Kupffer cells in Dog 25, although not present in enormous numbers, are nevertheless abundant, and represent phagocytic activity and hyperplasia of the endothelial elements as occurring late in the dog's infectious period. As the blood picture at this stage is slowly approaching a normal level, these histiocytes are approaching their resting state. In this dog we also find small periportal foci consisting of small lymphocytes with reticuloendothelial elements in the background. These are probably the result of lymphoblastic hyperplasia rather than an expression of inflammation, for newly formed collagenous fibers and other proliferative fixed connective tissue changes characteristic of chronic inflammation are not in evidence.

In Dog 268 a diffuse exudate is also observed in the liver consisting mostly of small and large round cells but with a considerable number of neutrophils. This can be sharply differentiated from the lymphoblastic foci of hyperplasia in Dog 25. The liver cords show extensive focal necrosis, confined more to the central and intermediate parts of the lobule. An attempt at fibrous repair is also in evidence. This condition has evidently developed from an extension of a splenic portal thrombophlebitis or from a general pyemia. The former is more likely, the primary focus being the multiple abscesses in the foreign-body tumor described above. The phago-

cytic activity in this dog is in harmony with the blood picture prior to death where an increased blood destruction with release of cellular débris leads to phagocytic stimulation.

Lymph Nodes. The lymph nodes show a hyperplasia of the endothelial and reticular elements. Eosinophils and plasma cells are very abundant. The follicles fail to stand out prominently. The reticuloendothelial cells appear in the sinuses, particularly in the medulla, as free active macrophages. In some instances the free macrophages in the sinuses are so numerous as to fill these channels completely.

Bone Marrow. There is a marked hyperplasia of all elements of the bone marrow, both of the stroma and the free cells in the meshes of the stroma (increased hematopoiesis). Conspicuous in the stroma is the undifferentiated cellular syncitium and typical phagocytic reticular cells or histiocytes (Fig. 8). Thin walled sinusoids are large and numerous. The littoral cells show considerable phagocytic activity; here and there they are seen rounded off and appearing as large free macrophages floating in the blood sinusoids. Only scattered single fat cells are found.

The various cell types of the hemopoietic tissue are irregularly scattered and mixed throughout the tissue. Most of the hemopoietic elements are young forms: erythroblasts and myelocytes with neutrophil, basophil and eosinophil granules. There are also large non-granular basophil cells of lymphoid nature, regarded as hemocytoblasts. Mature myeloid elements including the non-nucleated erythrocytes and the three types of granular leukocytes as they occur in the circulating blood are found everywhere between the other cells. Megakaryocytes are found scattered evenly among other elements. Some of them are enormous in size.

Lung. The early active infectious period (Dog. 1052) showed little change microscopically. Findings of exudative inflammation were wanting. In the later infective stage reticular elements were quite numerous and often filled with blood pigment. Free and fixed macrophages in the alveoli and interalveolar walls contain a varying number of hemosiderin and dark colored granules ("heart failure" cells).

Kidneys. Many of the glomeruli show necrosis with partial loss and disappearance of the glomerular structures. The endothelial cells of the glomeruli are for the most part swollen and the capillaries collapsed. The endothelium of Bowman's capsule does not show a proliferative action. Occasionally a small collection of serum is seen in the subcapsular space. The tubules show various stages of degeneration even to the point of complete necrosis (Fig. 9). The tubular epithelium where still present has lost its nuclear elements, contains fat droplets and appears flattened. The picture is that of a severe nephrosis with some involvement of the glomeruli. Perla and Gottesman[14] regard the severe nephrosis encountered in Bartonella muris infection as due, not to the severity of the systemic infection, but to the irritation incident upon excretion of large amounts of hemoglobin.

GROUP II. *Post Infection Period. Liver.* The liver shows focal necrosis confined principally to the center of the lobules around the central veins (Fig. 10). In these areas the cytoplasm contains abundant fat droplets. The Kupffer cells are small and normal in appearance, mostly in a resting state showing little phagocytic activity. Yellow brownish bile pigment is seen only in scattered intralobular capillaries. Here and there small collections of lymphocytes are encountered in the periportal areas. These foci are composed of small lymphocytes and seem to arise in the reticular tissue about the periportal areas.

Lymph Nodes. In these nodes the hyperplasia is not as pronounced as in those taken from the dogs autopsied during the acute infectious period.

The general picture, however, bears some resemblance as regards reticular and endothelial proliferation, the latter often blocking the sinuses and no doubt playing the rôle of active macrophages. With the abnormal blood destruction in these cases either partially or completely checked, the diminished cellular débris allows the excess number of active macrophages to revert to the resting or undifferentiated syncitium.

Bone Marrow. Hyperplasia of all the elements of the bone marrow is still observed, perhaps not in degree comparable to that encountered in the dogs of the anemic phase but nevertheless definitely marked. Erythropoiesis and myelopoiesis are prominently in the foreground. Megakaryocytes are present in abundance.

Lungs. In the lungs nothing of a striking nature is revealed. Reticular elements are somewhat numerous and some are seen carrying blood pigment in varying amounts. Localized collections of lymphocytes, conspicuous in the liver, are not so abundant in the lungs. They are seen in small numbers scattered about the bronchi. There is no evidence of inflammation. The peribronchial lymphocytic elements are not an expression of inflammation, but of lymphoblastic hyperplasia of the peribronchial lymphoid follicles.

Kidney. Several areas of lymphoblastic hyperplasia with reticular activity in the background are prominently displayed in kidney sections from Dog 312. The kidney structures otherwise present nothing abnormal. Replacement fibrosis of old tubular destruction occurs as the outstanding feature in Dog 24. The changes are confined chiefly to the collecting portion of tubules.

Dog 269 (control). The microscopic examination confined itself as in the other dogs to the liver, lymph nodes, bone marrow, lungs and kidney.

Liver. There is an apparent increase of Kupffer cells, which are mostly filled with trypan blue as are also the reticular cells found in increased numbers in the periportal areas. This hyperplasia dates back, no doubt, to the time of administration of trypan blue 10 months prior to splenectomy.

Lungs. In the lung there is a considerable accumulation of pigment peribronchially, but no further microscopic changes of note occur.

Lymph Nodes. Pigment deposit with replacement fibrosis is conspicuous throughout the section. Actual hyperplasia of reticular elements to a striking degree cannot be said to exist.

Bone Marrow. A moderate degree of hyperplasia was observed in the various elements of the bone marrow. It might be mentioned, however, that the actual amount of red type marrow found at autopsy in the usual sites of distribution was small.

Kidney. In the kidney section only one small area occurred where definite lymphoblastic and reticular activity was manifested. In scattered areas the tubules within a fibrous zone are atrophied and show various degenerative epithelial changes.

It must be admitted that from the evidence derived from the examination of one control dog, definite and adequate conclusions are impossible. The observations of Weicksel and Gebhardt[11] on a series of dogs, splenectomized, some a shorter—some a longer time (weeks, months, years) revealed nothing in the reticuloendothelial organs which appeared strikingly pathologic. The only finding that did not perhaps seem entirely normal to them was a moderate increase of Kupffer cells in the individual animals. They conclude, "that in dogs in which extirpation of the spleen dates back to more

than a month the increase of Kupffer cells in the liver is at least possible."

On the other hand, the accumulated experimental data of Pearce *et al.*[16] in reference to changes in the bone marrow, liver and lymph nodes of numerous splenectomized dogs, show that during the early periods, 1 to 3 months, the change in the marrow is slight. After the lapse of 6 months, however, the fat tends to be completely replaced by marrow cells. In the lymph nodes they found an increase of endothelial cells in a large proportion of dogs that had been splenectomized for periods of 2 weeks or more. The phagocytic Kupffer cells of the liver were in most instances also increased. The bone marrow hyperplasia they regard not as compensatory to the anemia caused by splenectomy, but rather as an expression of bone marrow actively in taking over the hemolytopoietic function of the spleen in its absence. The findings in the liver and lymph nodes also suggest the development of a compensatory phagocytic function for the loss of the spleen.

Discussion. Thus one finds that both the early and the late infectious periods are marked by changes confined almost exclusively to the reticuloendothelial elements of various organs. In the post-infection period these changes are still observed but here the picture is one of less activity and a reversion of the active differentiated phagocytic cells to the resting or undifferentiated elements. Furthermore, in examining blood smears one is struck by the excessive amount of cellular débris in the form of broken down erythrocytes present in the circulation. This blood destruction is dependent upon Bartonella organisms finding abode in the red cells. With the rapid blood destruction that follows their entrance and with the subsequent cellular débris accumulating in the circulatory blood, a mechanism for the removal of this débris is called into play, hence the enormous activity of the phagocytic endothelial and reticular cells throughout their principal sites of distribution.

The liver, lymph nodes and bone marrow being perhaps after the spleen richest in reticuloendothelial elements, it follows that phagocytic activity should be conspicuously demonstrated in these organs. In the liver this activity is manifested by the proliferation of the Kupffer cells. According to Maximow,[13] "the tortuous sinusoids of the liver are interposed between the portal and the hepatic veins so that the blood pressure is exceptionally low and the blood stream very low. Such an arrangement facilitates the removal of substances from the slowly passing blood and enables the Kupffer cells maximum opportunity to take up foreign particles."

The focal necrosis seen so conspicuously in the liver and to some extent in the kidneys and other organs may in all probability be explained by capillary thrombosis, leading to an ischemic de-

generation of dependent regional areas. Perla and Gottesman,[14] in studying the pathologic lesions of Bartonella muris in the lymph nodes, regard them as the result of hyperactivity and subsequent exhaustion of the endothelial elements. These same authors regard the two outstanding types of lesions in the kidneys, viz., focal necrosis and tubular degeneration as resultant upon endothelial destruction by the infectious process and excretion of hemoglobin and other irritating toxic substances of blood-cell destruction.

The marked hemopoietic activity in the bone marrow is the usual picture of regeneration seen in other severe grades of anemia. The severe anemia often developing in a short time leads to a state of anoxemia of the tissues with various progressive parenchymatous degenerative lesions, especially in such cellular organs as the liver and kidneys. The icteric tinting of tissues and hemoglobinuria encountered at the height of the Bartonella infection is but another manifestation of marked blood destruction and possible liver injury.

The persistent changes observed in the dogs free from an active infection for months and after they had recovered from a severe anemia may in all probability be looked upon as compensatory for the loss of the spleen. These changes are associated, no doubt, with immunity to further infection with Bartonella canis. Dog 24 could not on repeated attempts be reinfected 2 months after the last appearance of organisms in blood smears. Dog 269 (control), splenectomized 160 days prior to autopsy and free from organisms throughout this time, failed to show typical histologic compensatory changes. Perla[15] is of the opinion "that a compensatory mechanism to splenectomy develops only as a result of a physiologic need and in the absence of the Bartonella virus such a physiologic compensation for the protective action of the spleen does not develop." The compensatory changes are seen in the lymph nodes in the form of reticuloendothelial hyperplasia, in the bone marrow in the form of hyperplasia of all the tissue elements and in the liver and lung in the form of lymphoblastic collections periportally.

Summary. The course of Bartonella canis infection transmitted to 5 otherwise normal splenectomized dogs has been presented. The incubation period after injection with Bartonella in the different dogs varied from 7 to 15 days. During the infection cycle the organisms appeared and disappeared periodically from the blood stream. No definite regularity as regards sequence and duration of periodic attacks and intervals of freedom from organisms was observed in the individual dogs or in the animals as a group. Associated with the Bartonella infection was a progressive cyclical secondary anemia, leading to general emaciation and physical weakness. The animals recovered and the blood approached normal

levels as soon as the severity of the infection began to wane. No fatality occurred in our dogs.

The gross and histologic necropsy findings, of the chief reticuloendothelial organs in dogs during the active infection stage and after the infection had run its course are presented. Most striking is the marked phagocytosis in the active stage and changes compensating for the absent spleen in the later stage. A control dog is also included and reference is made to the histologic changes observed in simple splenectomized dogs by various workers.

A brief consideration of the activity of the reticuloendothelial elements occurring in Bartonella infection throughout their principal sites of organ distribution is given.

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THE PRESENCE OF THE INTRINSIC FACTOR OF CASTLE IN THE GASTRIC JUICE OF PATIENTS WITH PERNICIOUS ANEMIA.*

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Since Fenwick, in 1877, and Cahn and von Mehring, in 1886, called attention to the relationship of gastric secretion and pernicious anemia, there has been considerable speculation concerning the etiology of this disease. Recently, Castle, Townsend and Heath[1] postulated that an "intrinsic" factor was necessary for the development of a substance which caused red blood cells to mature, and that this substance was present in gastric juice obtained from apparently normal individuals, but absent in the gastric juice of patients with pernicious anemia. While this hypothesis is of the greatest importance, it does not explain adequately (1) the characteristic spontaneous remissions which occur in pernicious anemia; (2) why patients in relapse have variable red blood cell counts; and (3) why those patients with pernicious anemia who apparently have no "intrinsic" factor in their gastric juice are able to produce at least some mature red blood cells, despite the specific conclusion that the intrinsic factor must be present in order to accomplish this.

In an attempt to explain some of these questions, the following experiments were performed with gastric juice obtained from patients with pernicious anemia in relapse. The patients selected were proven to have pernicious anemia by their history, physical findings and laboratory procedures. The red blood cell counts were made on a Neubauer-Levy counting chamber (new ruling, U. S. Bureau of Standards). The hemoglobin was calculated in a Sahli hemoglobinometer according to the recently modified method of Osgood and Haskins. The reticulocyte counts were made on brilliant cresyl blue stained cover-slip preparations, and on each occasion 1000 red blood cells were counted.

Since the gastric secretion in pernicious anemia is markedly reduced in amount,[2,3] continuous aspiration of the stomach for 3-hour periods by means of a water suction pump (10 cm. mercury pressure) was necessary to obtain sufficient quantities of juice. The specimens were obtained under fasting conditions without histamin stimulation, as it was noted that this substance did not alter the gastric secretions in pernicious anemia. When the specimens were collected, sufficient concentrated hydrochloric acid was added to

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produce a hydrogen-ion concentration of pH 2, and the material was then stored in the icebox for variable periods of time. Gastric juice samples were obtained at intervals from 26 patients in relapse, and a total of 177 observations were made on the volume of gastric juice secreted per hour.

The average gastric-juice volume in the normal individual is approximately 150 cc. per hour.[3] In patients with pernicious anemia, the average gastric-juice volume was found to be approximately

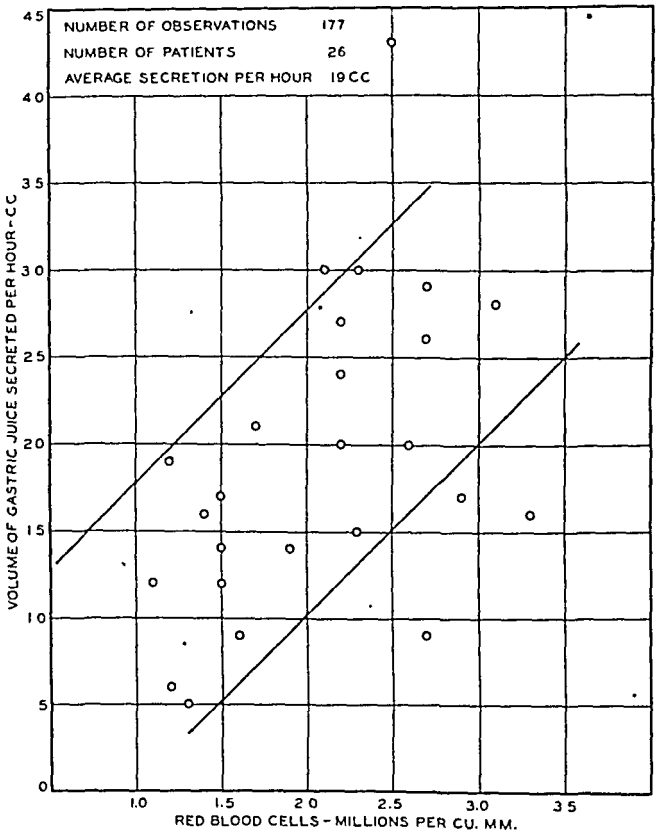


CHART I.—The relation between the average amount of gastric secretion and the red blood cell level in pernicious anemia (relapse).

20 cc. per hour, although there was considerable variation in individual patients. The extremes of gastric secretion were 4 and 45 cc. per hour. From the figures plotted in Chart I, it appears that in untreated pernicious anemia patients in relapse there exists a direct relationship between the amount of gastric juice secreted and the level of the peripheral red blood cell count. Consequently, it may be inferred that the blood stimulating factor of the gastric juice varies with the volume, and that with decreased gastric secre-

tion there is a corresponding decline in the red blood cell count. From these observations, it is suggestive that the so-called intrinsic factor in pernicious anemia is deficient in quantity rather than quality,[9] and the rate of hematopoiesis is dependent upon the quantity of intrinsic factor produced.[8]

In suggesting the previous conclusion, it has been assumed that the gastric juice obtained from patients with pernicious anemia contains the active principle or the so-called intrinsic factor. The following three experiments justify this conclusion.

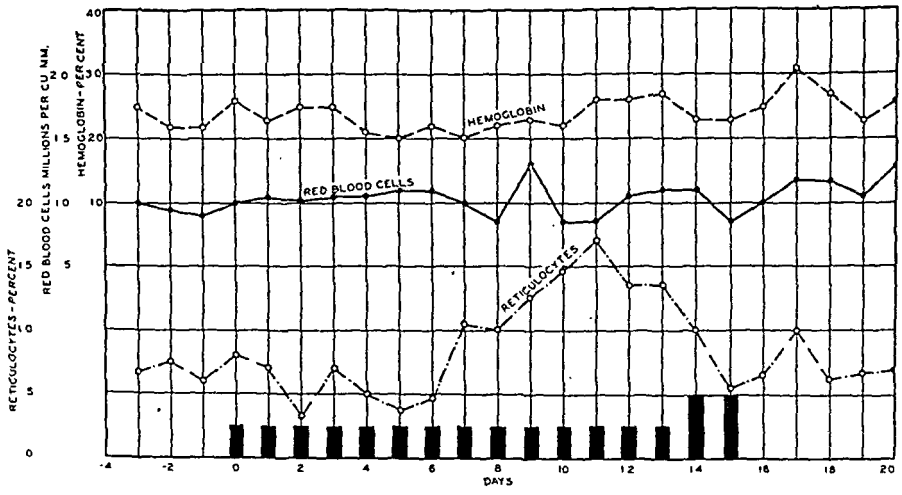


CHART II.—The effect on a case of pernicious anemia of the daily administration of pernicious anemia gastric juice incubated with beef steak.

Experiment 1. The gastric juice used in this experiment was obtained from 5 untreated patients with pernicious anemia in relapse (red blood cell counts varying from 1.5 to 3.3 millions per cmm.). It was collected during a period of 8 weeks and stored in a refrigerator until 1500 cc. had been obtained. A daily dose of 150 cc. of gastric juice was incubated with 200 gm. of meat for 2 hours, at pH 2 and later made pH 5. This was fed for 10 consecutive days to a patient with typical pernicious anemia, whose initial red blood cell count was 1.93 million per cmm. and hemoglobin 51% (Sahli) 7.14 gm.%. Table 1 shows that a rise in the percentage of reticulocytes started on the 10th day and reached a maximum of 9.8% on the 13th day. This was accompanied by an increase in the number of red blood cells and in the hemoglobin percentage. From the 10th to the 19th day no further treatment was given and the reticulocyte percentage fell to the pre-treatment level. This response[9] is similar to those which were previously reported as indicative of the presence of the intrinsic factor in normal gastric juice.[4]

Experiment 2. The preceding experiment was repeated in order to rule out the possibility of a spontaneous remission. The procedure varied slightly in that the gastric juice feedings were given over a longer period of time. For a period of 12 weeks gastric juice was collected from 10 patients with pernicious anemia in relapse. A total of 2545 cc. was obtained. For 13 consecutive days, the subject (pernicious anemia in relapse) ingested

150 cc. of gastric juice incubated with beefsteak, and for the last 2 days the dosage of gastric juice was doubled. Chart II shows that a rise in the reticulocyte percentage started on the 7th day and reached a maximum of 16.2% on the 11th day. A secondary rise of the percentage of the reticulocytes occurred on the 3d day after the dosage of gastric juice was doubled.

TABLE 1.—THE EFFECT ON A CASE OF PERNICIOUS ANEMIA OF THE DAILY ADMINISTRATION OF PERNICIOUS ANEMIA GASTRIC JUICE INCUBATED WITH BEEFSTEAK.

Date (1934)	R. B. C. (million per cmm.)	W. B. C. (per cmm.)	Hemoglobin (%)	Reticulocytes (%)	Day of treatment.	Type of treatment.
1/ 9	2.3	5600	57	...	–3	
1/10	1.93	4200	51	2.7	–2	
1/11			..	5.2	–1	
1/12			..	1.8	0	150 cc. of gastric juice plus 200 gm. beefsteak.
1/13			..	5.7	1	" " "
1/14			..	5.2	2	" " "
1/15			..	4.6	3	" " "
1/16			..	3.5	4	" " "
1/17			..	4.0	5	" " "
1/18			..	3.5	6	" " "
1/19	1.85	5000	49	5.3	7	" " "
1/20			..	5.2	8	" " "
1/21			..	3.8	9	" " "
1/22			..	6.5	10	
1/23	1.76	4800	52	8.1	11	
1/24			..	9.4	12	
1/25			..	9.8	13	
1/26	2.29	6100	60	6.3	14	
1/27			..	6.5	15	
1/28	2.31		60	6.8	16	
1/29			..	7.3	17	
1/30	1.95		56	5.0	18	
1/31			..	4.2	19	
2/ 1	2.19	6950	61	5.7	20	

The results obtained in these 2 experiments are most suggestive of the fact that pernicious anemia gastric juice contains the active principle, and the presence of this substance accounts for the limited hematopoietic activity which did occur in the two experiments just described.

Experiment 3. If the intrinsic factor in reduced amounts is present in the gastric juice of patients with pernicious anemia, it was thought that additional information bearing on this question might be obtained by the following procedure: obtain a relatively large amount of gastric juice from a patient with pernicious anemia in relapse and then administer it to the same patient for a short interval in concentrated form. Daily specimens were obtained by aspiration of the gastric secretions for a period of 20 days. A total of 760 cc. were collected. Because of the small amount it did not seem practical to administer it orally; and since previous investigators[5,6] had proven the effectiveness of intramuscular injections of normal gastric juice, this method was chosen. The gastric juice was concentrated

under reduced pressure to 12 cc. This amount was divided into two equal doses and given on successive days. At the onset of treatment, the red blood cell count was 2.6 millions per cmm. and the hemoglobin 76%. Chart III shows an initial increase of the reticulocytes on the second day, a maximum peak of 7.4% on the 10th day and then a return to the pre-treatment level. Since there are no standards by which to compare this response, it can only be concluded that pernicious anemia gastric juice contains the intrinsic factor. If one wishes to compare the results with the reticulocyte standard of oral administration of liver extract or desiccated stomach,[7] the peak in this experiment reached the calculated response for this individual.

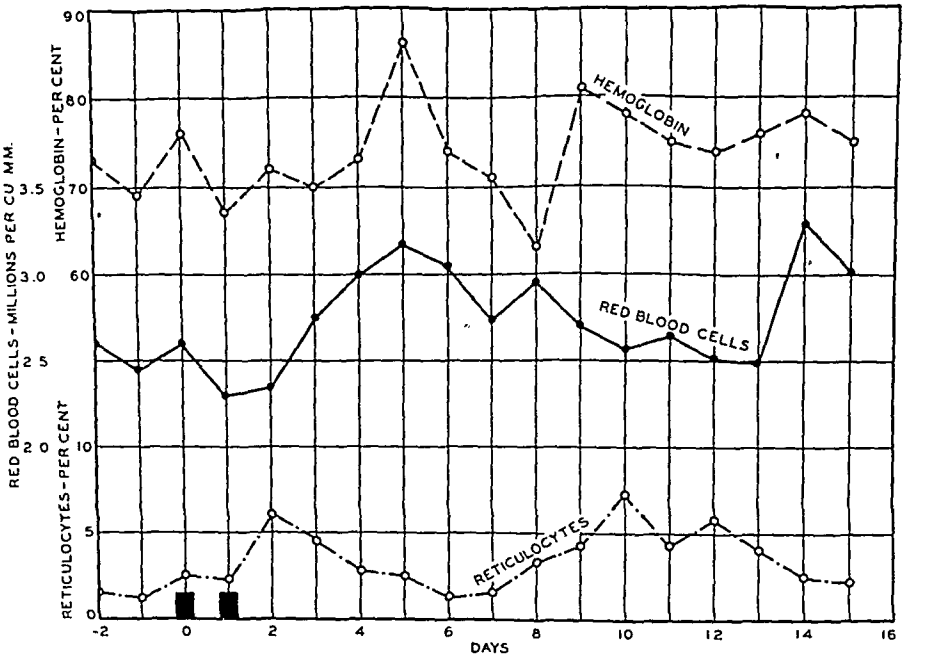


CHART III.—The effect on a case of pernicious anemia of two intramuscular injections of the patient's gastric juice (concentrated).

From the experiments described, it appears possible to explain why patients with pernicious anemia are able to maintain a limited amount of hematopoietic activity, and why different patients have different rates of red cell formation. Apparently erythropoiesis depends in part, at least, upon the action of the intrinsic factor, and the rate of red blood cell formation is related to the amount of the intrinsic factor produced. Spontaneous remissions still remain in the realm of speculation.

Conclusions. 1. The intrinsic factor of Castle is present in the gastric juice of patients with pernicious anemia in relapse.

2. The deficiency of the gastric secretion in pernicious anemia appears to be quantitative rather than qualitative.

3. The red blood cell count, in relapse, falls to a level determined by the amount of intrinsic factor which the patient is able to secrete in his gastric juice.

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THE TREATMENT OF CORONARY ARTERY DISEASE BY INTRAVENOUS INJECTIONS OF HYPERTONIC SALINE SOLUTION.

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The favorable results achieved by Silbert[1] in the treatment of patients suffering from thromboangiitis obliterans, by repeated intravenous injections of hypertonic saline solution, suggested the possibility of applying the same principle of therapy to arterial disease of the heart. Silbert administers hypertonic salt solution in 300 cc. doses intravenously, 3 times weekly. Patients so treated soon lost their pain. Although the disease process differs essentially in coronary sclerosis, the therapeutic objective, the development of collateral circulation, is identical in the two conditions.

The author harbored this belief for 6 years, but feared to give intravenous saline injections to patients with coronary artery disease. Three years ago, however, an opportunity occurred to observe the effect of this therapy. A patient having arteriosclerotic closure of the leg vessels and coronary disease, was given intravenous therapy accidentally before a cardiac examination was made. Three

injections of 5% sodium chlorid solution of 300 cc. each had been given to the patient before the diagnosis was known. A cardiac study then revealed that he had had a coronary thrombosis 10 years previously. Since that time he had been unable to walk more than 5 to 6 city blocks. Beyond this distance he was stopped by precordial pain. His electrocardiogram taken on February 15, 1932, showed a diphasic *T* wave in Leads I and II (Fig. 1). Because his precordial pain on walking completely disappeared on the first 3 injections, the intravenous injections were continued. During the following 3 years of this treatment he had only one episode of angina. This occurred after the patient had an altercation with members of his family. The attack lasted only 1 day. At the present time he receives a weekly injection of 300 cc. of a 5% solution of sodium chlorid. Today he can walk any distance without symptoms.

During this 3-year period 15 other patients with combined arteriosclerotic closure of leg vessels and coronary artery disease have been treated with intravenous injections of hypertonic salt solution. No untoward accident has occurred. The results in these 15 cases appeared so promising that 6 intractable cases of angina pectoris due to coronary artery disease without arterial involvement of the extremities were selected for special study. The group consisted of 5 cases of angina pectoris following coronary artery thrombosis and 1 case of coronary sclerosis in a diabetic. These patients had had coronary artery disease for at least 6 months and had not improved under the ordinary course of treatment, which consisted of a restricted diet, cessation of smoking, drugs when indicated, physiotherapy and prolonged rest. None of the 6 patients could walk one block without being stopped by precordial pain or dyspnea.

THERAPY: The initial dose was 100 cc. of a sterile 5% sodium chlorid solution. Subsequent doses were increased by 50 cc. weekly up to a maximum of 250 cc. Injections were given 3 times weekly. If precordial pain occurred during, or immediately following, the increased intravenous injection, it was evident that the heart was not ready for it. The author continued the therapy with the previous dose for a period of 3 weeks. The increased dose was then retried and was in every case successful. A graduated 300 cc. burette was used and the solution was given intravenously by gravity. The burette was about 3½ feet above the patient who was lying horizontally. Patients were not hospitalized and came to the clinic unattended. Minor untoward reactions occurred in the treatment which will be noted in the clinical description of each patient. These patients did not receive any drugs or other treatment after the intravenous injections were begun.

Case Reports. CASE 1.—P. A. (Hosp. Chart No. 361748), white, male, Puerto Rican, cigarmaker, aged 46, had been on the wards of this hospital twice. The date of his last discharge was February 10, 1934. He was admitted to the hospital for the second time because of severe precordial pain and dyspnea on exertion. A Roentgen ray examination of the left shoulder showed calcific deposits in the region of the left subdeltoid bursa. The discharge diagnosis was coronary thrombosis, coronary sclerosis and chronic left subdeltoid bursitis. For 6 months following his discharge from the hospital he was practically confined to his home because he was unable to walk one block without dyspnea on exertion. He came to the dispensary with the greatest difficulty, not only for treatment of his heart, but also for the pain in the left upper extremity. Neither the heart nor the left upper extremity improved by the ordinary methods of therapy for 6 months.

Physical examination before initiating the intravenous therapy showed: *Heart:* left border in the fifth interspace 8 cm. from the midsternal line. Sounds are of poor quality, regular, 80; no murmurs. Blood pressure 110/80. *Lungs:* clear. No evidence of decompensation. He was unable to move his left upper extremity due to subdeltoid bursitis.

Intravenous therapy was begun on August 17, 1934, with 100 cc. of 5% sodium chlorid solution. The plan outlined above was followed. After the 5th injection the patient was able to raise the left hand a short distance from his side. The improvement continued slowly so that after the 15th injection, he was able to raise the left upper extremity above his head without pain. There has been no recurrence of this pain up to date. The spasm of the left upper extremity was a manifestation of coronary artery disease.

He noticed that he was able to walk two blocks without dyspnea after the 6th injection. Here again improvement has progressed steadily. At the present time he can walk from 10 to 15 city block without symptoms. A point of interest was the precordial pain which occurred when the dose was raised to 250 cc. This pain lasted an hour. Taking this as a danger signal, the dose was returned to 200 cc. for 2 weeks. Then when the 250 cc. dosage was again tried, no precordial pain ensued. At present he gets 250 cc. twice a week. His electrocardiogram gave evidence of myocardial damage (Fig. 2).

CASE 2.—A. G. (Hosp. Chart 359000), Russian Hebrew operator, white, male, aged 48, had been in the wards of this hospital on 3 occasions. He was discharged on November 18, 1933, with the diagnosis of coronary artery thrombosis and coronary sclerosis. On his last hospital visit a venesection was done because of heart failure. For 9 months following the last discharge from the hospital, his time was largely spent in convalescent homes. He was unable to walk up a flight of stairs because of angina pectoris and dyspnea and could only walk one block on level ground.

Physical examination of the chest before saline treatment was started, was: *Heart:* the left border was in the fifth interspace 9 cm. from the midsternal line. Sounds were regular, fair, 92; soft apical systolic murmur. Blood pressure was 140/100. *Lungs:* clear. No evidence of decompensation. His electrocardiogram is shown in Fig. 3.

Intravenous therapy was begun on August 17, 1934, with 100 cc. of 5% sodium chlorid solution. The same procedure was followed as outlined. On the 7th injection, he found he could walk two blocks without distress. He experienced no cardiac complaint under a steadily increasing dosage. After a month's treatment he was able to walk 4 blocks without distress. After 9 months' treatment his range of activity is from 4 to 8 city blocks.

CASE 3.—A. B. (Hosp. Chart No. 363119), Russian Hebrew tailor, white, male, aged 63, has been in and out of the hospital wards many times during the past 12 years. When his attacks of precordial pain with radiation down

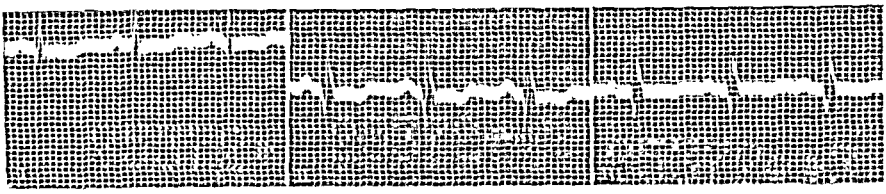


FIGURE 1

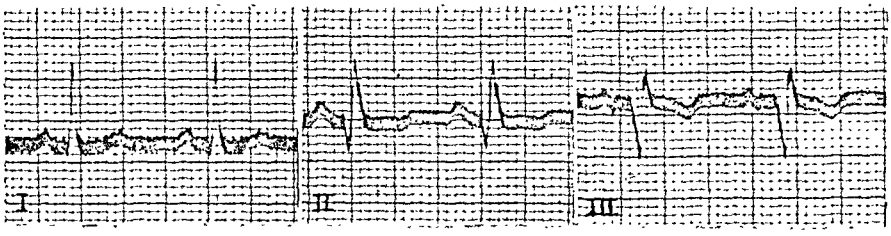


FIGURE 2

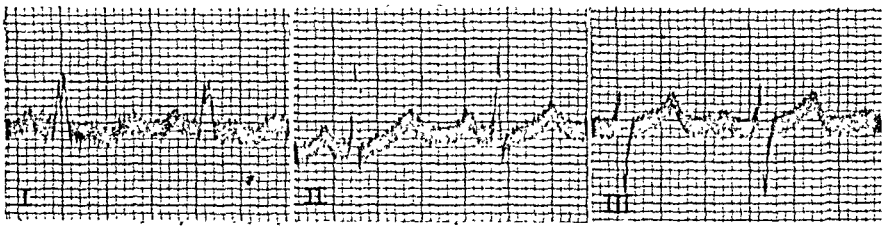


FIGURE 3

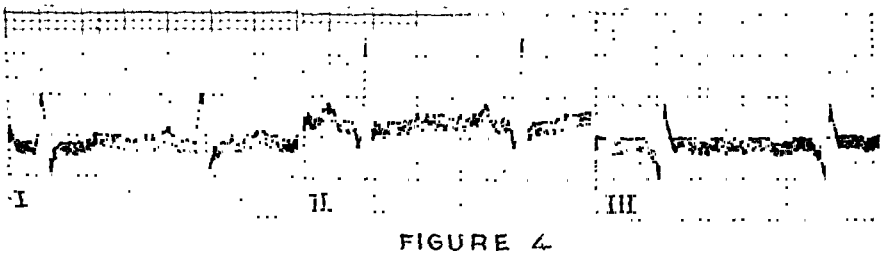


FIGURE 4

FIG. 1.—*T* waves in Leads I, II and III diphasic. *Q* waves in Leads II and III deep.
FIG. 2.—*T* wave in Lead I low, diphasic in Lead II, and inverted in Lead III. *Q* wave in Leads II and III large.
FIG. 3.—*T* wave in Lead I diphasic. *Q*–*R*–*S* notched and slurred in all leads.
FIG. 4.—*T* wave in Lead II low and diphasic in Lead III. *Q* wave in Lead III deep.

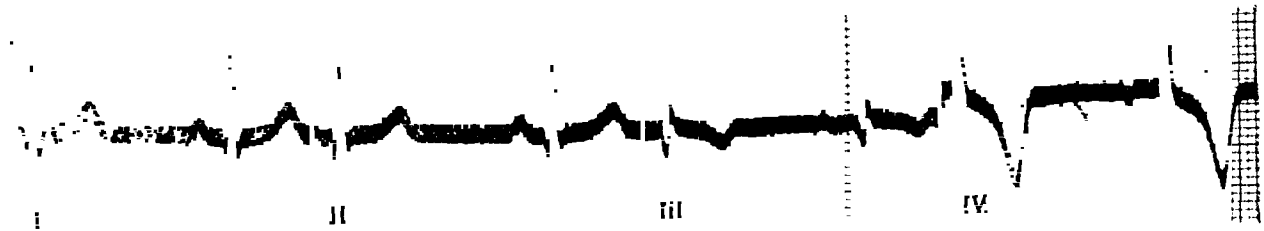


FIGURE 5

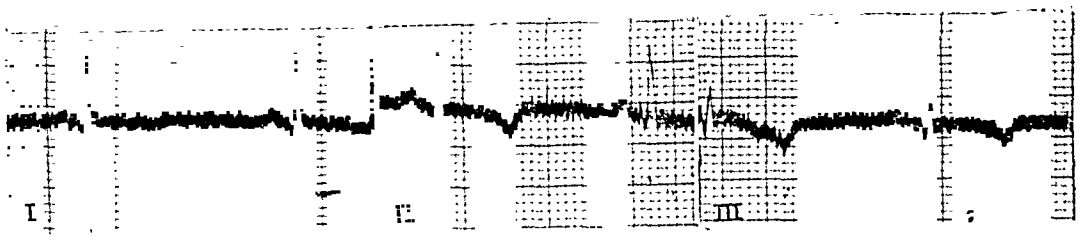


FIGURE 6

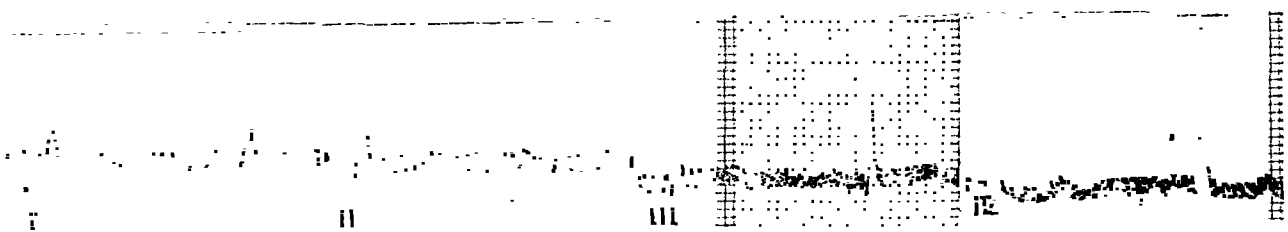


FIGURE 7

FIG. 5.—*T* wave in Lead III inverted. *Q* wave in Lead III deep. *T* wave in Lead IV very prominent. This electrocardiogram is not conclusive. The diagnosis of coronary artery thrombosis and sclerosis was made on the clinical course of the case.

FIG. 6.—*T* wave in Lead I flat, inverted and cove plane in Lead II, and inverted in Lead III.

FIG. 7.—*T* waves of low voltage in all leads, and upright in Lead IV.

his left arm became too severe, hospital care resulted in the amelioration of symptoms. Two and a half years ago, it was noted that he had sugar in his urine and since then he has been under a special dietary regimen. During the past 6 months he has been unable to walk a block without having excruciating, clamping precordial pain. He was compelled to take to bed during this period at least 3 times a week. Nitroglycerin was the only drug which relieved him.

Intravenous therapy was started on August 17, 1934. This patient first noticed improvement about 2 weeks after the therapy was begun. In the course of treatment he was able to walk to the hospital which was 5 blocks away from his home without experiencing pain or other symptoms. The treatment was stopped for a period of 5 weeks because jaundice developed. But after this cleared up, treatment was resumed. At present he gets 200 cc. of the solution twice a week and is able to walk 6 city blocks without pain.

His electrocardiograms never showed any abnormality until recently; on March 14, 1935, it showed a definite change (Fig. 4).

CASE 4.—J. E. (Hosp. Chart No. 373916), Russian Hebrew, operator, white, male, aged 40, was discharged from the wards of this hospital on April 15, 1934, with the diagnosis of coronary thrombosis and coronary sclerosis. Up to the time of instituting saline therapy, an interval of 7 months, he was unable to leave his home because he experienced angina pectoris after walking 1 block. The Master step test confirmed the patient's disability; he was unable to complete the 22 mounts required of him according to his height, weight, age, and sex. He stopped after 5 mounts because of precordial pain.

His chest findings before treatment was begun were: *Heart:* the left border of the heart was in the fifth interspace 9 cm. from the midsternal line. The sounds were poor, regular, 76; no murmurs. Blood pressure was 130/80. *Lungs* are clear. There was no evidence of decompensation. Electrocardiogram (Fig. 5).

Intravenous therapy was begun on November 17, 1934, with a 100 cc. dose. An obstacle in the ambulatory treatment was the great distance the patient had to travel to the hospital. He came to the dispensary from his home completely exhausted and suffered extreme angina pectoris. In order to build up his cardiac reserve he was admitted to the wards of the hospital and remained there 2 weeks. On the wards he received a daily intravenous injection of 100 cc. The Master step test demonstrated his improvement, for he was able to complete the 22 mounts without distress. Ambulatory treatment was again resumed but during the following 3 months he was taken to the dispensary by automobile. However, he returned home on foot. Under treatment his improvement progressed steadily. He can now climb the subway stairs slowly with no difficulty. At present he can walk from 10 to 15 blocks without symptoms.

CASE 5.—O. S. (Hosp. Chart No. 371843), Russian Hebrew, white, male, aged 55, was admitted to the wards of this hospital twice. The final note on his first visit on October 3, 1931, showed that he had arterial hypertension of 3 years' standing and had been admitted after 10 months of increasing attacks of precordial pressure, orthopnea, and dyspnea. His electrocardiogram showed cover-plane *T* waves in Leads II and III. He was readmitted to the wards on October 7, 1934, giving an interval history of being followed in the cardiac clinic since his first hospitalization. He felt somewhat better at times during the 3 years, but for the past 6 months he was repeatedly seized with excruciating precordial pain radiating to the back. These attacks were relieved by nitroglycerin tablets. During the attacks he was obliged to sit up in bed and gasp for breath. The date of discharge after his second hospital visit was October 20, 1934.

Intravenous therapy was begun on December 15, 1934, with the initial dose of 100 cc. After 2 weeks of treatment he found he was able to make the journey from his home to the dispensary, 5 blocks away, despite the fact that he had slight precordial oppression. His improvement has progressed slowly. He now receives 2 injections a week. He experienced no chest symptoms on increasing the amount of hypertonic salt solution. Since the fourth dose, about 5 months ago, he has had only 2 severe attacks of precordial pain. He can walk 5 to 10 blocks at present.

His electrocardiogram is shown in Fig. 6.

CASE 6.—F. R. (Disp. Chart No. 33–9226), Russian laborer, white, male, aged 55, was admitted to the dispensary on June 7, 1933, giving a 2 years' history of precordial pain with radiation down the left arm. An electrocardiogram at this time showed a cove-plane *T* wave in Lead I and a slightly inverted *T* wave in Lead II. He was treated at the cardiac clinic in routine fashion for 1½ years but was unable to walk 1 block without severe precordial pain. He took 7 to 8 nitroglycerin tablets a day to relieve the attacks.

Physical examination of his chest before intravenous injection showed: *Heart:* left border in the fifth interspace 9 cm. from the midsternal line. Sounds are poor at the base but are better at the apex. Rate 84; no murmurs. Blood pressure 135/90. *Lungs* are clear. Electrocardiogram on November 3, 1934 (Fig. 7).

Intravenous injections were begun on October 13, 1934, with 100 cc. of the solution. He first noticed that he could walk 2 blocks without angina after the 5th injection. The increasing dosage produced no chest complaints. His improvement has continued until now, after 6 months' treatment, he can walk from his home, 20 blocks away, to the dispensary.

Discussion. These 6 patients with angina pectoris were selected for treatment with intravenous injections of hypertonic salt solution because they were definite and uncomplicated cases of coronary artery disease whose symptoms had not been relieved by the usual forms of therapy. Striking improvement occurred in all. It might be contended that the good results obtained in these cases were on a psychogenic basis. These patients are usually heart conscious and their cardiac status may be improved temporarily by psychotherapy, but clinical experience proves that the pain soon returns. Harlow Brooks,[2] in a recent talk, stated that in his experience, which is large, autosuggestion in true angina was of no permanent value.

It may also be admitted that spontaneous remission of anginal pain and other symptoms may occur under any form of treatment or even without treatment other than a period of rest. The cases employed for this therapeutic experiment were selected because they had all failed to improve spontaneously over long periods of observation in spite of rest, sedatives, and the customary therapeutic procedures.

No claim is made that the arteriosclerotic process responsible for this disease is arrested. The treatment was employed in an attempt to increase the collateral circulation. By postmortem injections Gross[3] has shown that remarkable degrees of collateral circulation may develop in the heart following occlusion of a coronary vessel. He states that the functional condition of the heart

after a coronary occlusion depends upon the richness of the collateral circulation which subsequently develops. The intravenous administration of large amounts of hypertonic salt solution probably favors the development of collateral circulation through the finer ramifications of the coronary system.

Contraindications. In selecting the first cases, care was taken to avoid those that showed: 1, Nephritis; 2, cardiac decompensation; 3, cardiac arrhythmia (except extrasystoles and sinus arrhythmia); 4, arterial hypertension over 180 mm. of mercury. Only further experience will show whether all four must be regarded as definite contraindications to the treatment.

Summary and Conclusion. 1. Six patients with severe and intractable angina pectoris due to coronary artery disease who were seriously incapacitated and had not improved on rest and customary therapy, were treated with repeated intravenous injections of hypertonic saline solution over long periods of time.

2. Definite and continuous improvement has been noted in their clinical condition.

3. The hypothesis is presented that the clinical improvement may be due to the fact that the treatment encourages a more rapid development of collateral circulation in the heart wall.

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CARDIOMEGALIA GLYCOGENICA CIRCUMSCRIPTA.*

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Hypertrophy of the heart in infants due primarily to massive deposition of glycogen has been recognized only within the past few years, and has been regarded as representing a cardiac type of von Gierke's glycogen storage disease. The few cases heretofore reported have shown diffuse involvement of the myocardium. However, the possibility that there exists general hypertrophy of the heart associated with localized glycogen deposits not of neoplastic origin, must be thought of in view of the case of Carrington and Krumbhaar,[1] discussed below.

* Read before the 27th Annual Meeting of the Undergraduate Medical Society of the University of Pennsylvania, April 25, 1935.

Von Gierke's disease, first described in 1929, is a disease of young children characterized by the abnormal accumulation and storage of glycogen in the parenchymal cells of various organs, together with enlargement of one or more of the affected organs. A tremendously enlarged liver and very large kidneys were found by von Gierke[2] in each of his 2 patients. He concluded that he was dealing with some metabolic disturbance, and likened the disorder to the lipoid deposit diseases of Gaucher and Niemann-Pick.

In 1932, Bischoff[3] and Putschar[4] presented the clinical and necropsy findings respectively in a case in which the most markedly involved organ was the heart. Subsequently, Pompe,[5] also, described a case with glycogenic cardiac hypertrophy, without enlargement of the liver. It soon became apparent that there were at least two essential forms of the disease, the hepatomegalic and the cardiomegalic. Of the latter, 10 cases are now accepted as proved.[6]

In the cardiac type the heart may become very greatly enlarged.[4,5,6,7] The myocardium is described as pale, brownish or reddish-pink with possibly grayish streaking. No definite changes have been found in the pericardium, endocardium, valves, aorta or coronary arteries. The histologic picture is striking, for the entire myocardium presents a mesh or network appearance. The spaces of the mesh are of varying sizes and shapes, and the walls are seen, under high power, to be composed of striated fibers. Antopol, Heilbrunn, and Tuchman[7] state that in tangential section the muscle cells appear in the form of "hollow cylinders surrounded by delicately striated protoplasmic walls." The nuclei are usually located at the periphery of the cells. According to Humphreys and Kato,[6] the length of the muscle fibers is from 2 to 4 times normal. Some perivascular fibrosis and thickening of the endocardium have occasionally been reported. Best's carmine stain reveals that the vacuoles are filled with glycogen granules, some being present also in the interstitial tissue but none in the nuclei. Fat stains are invariably negative.

The storage of glycogen may occur in many other tissues. It is interesting to note that in one instance of skeletal muscle involvement not all the fibers were affected to the same degree. Many normal ones were interspersed between vacuolated, glycogen containing fibers.[6]

Pompe[5] was the first to point out that diffuse rhabdomyomatosis and so-called idiopathic hypertrophy of the heart may be manifestations of the cardiomegalic type of glycogen storage disease. Rhabdomyomas are known to contain abundant glycogen.[8] These tumors, which may occur either as single or multiple nodules in the myocardium, or in a more diffuse form, are sometimes said to have a microscopic appearance resembling that found in von Gierke's disease. Pompe cites several such instances, and has even suggested that rhabdomyomas arise on the basis of a disturbed

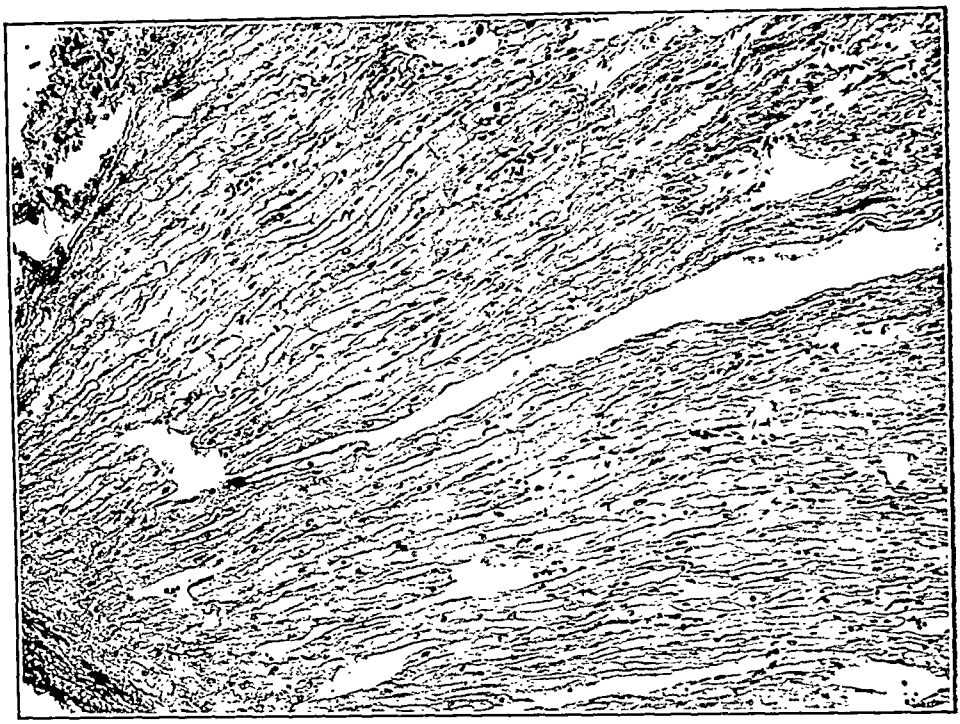


FIG. 1.—Photomicrograph of cardiac muscle showing area of vacuolization. Low-power view.



FIG. 2.—Photomicrograph of section from the original block of myocardium after staining with Best's carmine stain. Glycogen is represented by the red staining dots which here appear black. Most of the glycogen has evidently been washed out because of the formalin originally used as the fixing medium. High power view.

metabolism and are not neoplastic.[5] However, the histopathology, as discussed in detail by Wolbach[9] and as reviewed recently by Farber,[8] is quite distinctive and dissimilar.

For the unusual condition of so-called idiopathic hypertrophy of the heart in children no adequate explanation of the cause has been given. But at least 1 such case, that of Sprague, Bland and White[10] has been found to belong to the cardiac type of von Gierke's disease (Humphreys and Kato[6]).

In 1924, Carrington and Krumbhaar[1] described a case of idiopathic hypertrophy of the heart the histology of which suggests glycogen storage disease. The patient, a female child of 10 months, was found clinically to have a large heart and a palpable liver and spleen. Two months later she died of a bronchopneumonia, and the large heart was brought to Dr. Krumbhaar for pathologic examination.

At necropsy the heart was found to be greatly hypertrophied, with some dilatation of the left side, weighing 136 gm. instead of the normal for that age of about 35 gm. The endocardium was slightly thickened, the valves were thin and competent, and both the foramen ovale and the ductus arteriosus were closed. The left coronary artery had an anomalous origin from the pulmonary artery just above the posterior cusp and nourished distinctly less than half the heart. Though grossly no differences were observed in different parts of the myocardium, microscopic examination disclosed areas of large wavy muscle fibers showing what was reported as "vacuolar degeneration." This was most marked in the areas supplied by the anomalous artery (Fig. 1). Elsewhere the fibers were large with large rectangular nuclei. A slight diffuse fibrosis was also present in some places. No glycogen or fat stains were made.

The liver was somewhat enlarged, weighing 384 gm., the normal being about 275 gm., and microscopically revealed a fleecy shreddy appearance of the cells. Moderate inflammatory changes were noted in the kidneys.

In view of the possibility of this being a case of glycogen storage disease because of the degree of vacuolization, it was desirable to review the original tissues in the light of more recent knowledge. Reëxamination of the old slides and of newly cut sections from the heart shows many areas of vacuolization both in the walls of the ventricles and in the papillary muscles. Under high power the muscle cells are seen to be large and distended but empty, with no particular changes in the nuclei. The large empty spaces do not resemble those produced by fatty change when a comparison is made with a fatty heart. Certain areas appear to be similar to less extensively involved areas in sections from the proven case of Antopol, Heilbrunn and Tuchman, and are almost identical with the descriptions and photographs of various other authors. Both fat and glycogen stains were made and found to be negative, but this

was to be expected since the gross specimen had rested in preserving solution over 13 years.

As a final measure new sections were cut from the old paraffin blocks in which the tissues had been imbedded, and stained with Best's carmine stain. In the vacuolated areas there can now be observed numerous small, discrete, red stained granules which are present both in the empty spaces and in the remaining substances of the muscle fibers. There are also small granules scattered in the scattered in the adjacent and apparently non-affected, *i. e.*, non-vacuolated, portions and in the interstitial tissue (Fig. 2). Consequently, we are able to say that there is a definite deposition of glycogen in this heart. Even in these preparations there was ample opportunity for much of the glycogen to be dissolved postmortem. We have, therefore, a heart with many localized areas resembling vacuolization which can be shown by means of the carmine stain to contain glycogen. The histology in these parts is not at all like that of a rhabdomyoma but rather resembles that of glycogen storage disease.

The anomalous coronary artery and the mild renal changes were regarded in the original report[1] as insufficient cause for the tremendous general hypertrophy. The possibilities that present themselves are:

1. This case may represent a localized cardiac type of von Gierke's disease. The etiologic factor might be ascribed to a congenital anomalous failure of, or retardation in, the development of the local glycogenolytic enzymes in late fetal life, the "dysontogenetic hypenzymatosis" of von Gierke,[2] or to a localized failure of ontogenetic myocardial development subsequent to "persistance of the fetal type of glycogen metabolism."[7] As congenital anomalies are often multiple, the presence of the anomalous artery lends color to the congenital anomaly concept. The uninvolved areas may be compared to the uninvolved fibers in skeletal muscle in Humphreys and Kato's case cited above.[6]

2. It may represent a stage of recovery in von Gierke's disease.

3. It may be a consequence of the abnormal blood supply from the anomalous artery, or, 4, Glycogen accumulation may be added to the list of possible causes of idiopathic hypertrophy. The histopathology may then be said merely to simulate that of glycogen storage disease.

In the future such cases with areas of apparent vacuolization should be tested for the presence of glycogen.

The descriptive term *cardiomegalia glycogenica circumscripta* is suggested to differentiate this condition from the more diffuse involvement in a typical case of cardiomegalic glycogen storage disease.

Summary. 1. A case of idiopathic hypertrophy of the heart, reported in 1924 by Carrington and Krumbhaar, is reviewed. His-

tologically the myocardium showed many areas of apparent vacuolization similar to those found in the cardiac type of von Gierke's disease. Moreover, the presence of glycogen can be demonstrated in this specimen.

2. Such localized deposits of glycogen in an otherwise unexplained hypertrophy of the heart may represent a localized form of von Gierke's glycogen storage disease, or a healing stage of that disease, or merely a cause of idiopathic hypertrophy.

3. The descriptive term "cardiomegalia glycogenica circumscripta" is suggested for this condition.

My thanks are due to Dr. Krumbhaar for the opportunity to study this material in his department and for suggestions during the course of the study.

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BOOK REVIEWS AND NOTICES

HUMAN PATHOLOGY. A Textbook. By HOWARD T. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland. With an Introduction by SIMON FLEXNER, M.D. *Pp. 1013; 433 illustrations*, 18 in color. Fourth edition, revised. Philadelphia: J. B. Lippincott Company, 1935. Price, $10.00.

IN the new edition of this standard textbook the chapter on the general pathology of tumors has been completely rewritten, and the sections on the hematopoietic system, the ductless glands and nervous system have been revised and brought up to date. Three hundred references have been added to the bibliography. It is gratifying to note that the excellence of the work has been fully maintained. M. McC.

A BIBLIOGRAPHY OF TWO OXFORD PHYSIOLOGISTS, RICHARD LOWER (1631–1691) AND JOHN MAYOW (1643–1679). By JOHN F. FULTON, M.A. (OXON.), Sterling Professor of Physiology in the Yale University School of Medicine. Pp. 62; 7 illustrations. Oxford: University Press, 1935. (No price given.)

A WELCOME successor to the author's bibliography of Robert Boyle, this book describes 42 editions of Lower's 5 major works and 18 editions of Mayow's 3 books. In continuation of the idea of humanized bibliography, Dr. Franklin's Introduction and the author's Preface and Epilogue give a background and sidelights that bring these two Oxford physiologists clearly before us. Mayow, in agreement with Paterson's views, is portrayed as the uncritical popularizer; Lower as the independent and brilliant investigator. The valuable point is also emphasized that "scientific ideas should be considered in relation to the soil from which they grow."

E. K.

AGENTS OF DISEASE AND HOST RESISTANCE. Including the Principles of Immunology, Bacteriology, Mycology, Protozoölogy, Parasitology and Virus Diseases. By FREDERICK P. GAY, in association with 19 others, all of whom, except 4, are past or present members of the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York. Pp. 1581; 212 illustrations, 6 colored plates, 125 tables and 61 diagrams. Springfield, Ill.: Charles C Thomas, 1935. Price, $10.00.

THIS extensive treatise by Professor Gay and his associates deals with the etiology of disease in its broadest sense. As stated in the Preface, attention has been centered on principles rather than practice, that is to say, the book contains almost no detailed information as to the technique of the laboratory sciences with which it deals. Since there are a number of excellent manuals on technique, the omission of details of methods allows the inclusion of subjects not usually brought together in book form. The work consists of 12 parts divided into 65 chapters. In the first 5 parts (pp. 1–454) are discussed the general aspects of the causation, classification and nature of disease; inanimate disease agents and tolerance; the morphology and physiology of living disease agents, particularly bacteria;

infection and epidemiology; and resistance and immunity. The sixth and largest part (pp. 455–1070) deals with pathogenic bacteria and diseases produced by them; the seventh with pathogenic spirochetes and spirochetoses (pp. 1071–1108); the eighth with pathogenic fungi and fungus diseases (pp. 1109–1151). In Part IX (pp. 1152–1274) are a number of chapters on filterable viruses and related pathogenic forms. In Part X (pp. 1283–1435) the animal pathogens are treated; with chapters on the pathogenic protozoa, on helminths, and on arthropods as agents and vectors of disease. The next part (pp. 1436–1466) which in the Reviewer's opinion should either be omitted or expanded) discusses diseases of obscure etiology. In the final part (pp. 1467–1562) are presented practical results in the diagnosis, prevention and cure of infectious diseases.

A good selected bibliography is given at the end of every chapter. Over 200 illustrations, some of them colored, and numerous well-arranged tables and diagrams add to the value of a book which will serve not only as an excellent text for the advanced student of bacteriology and allied sciences, but also as a modern presentation of subjects of great importance to the practitioner of medicine who stands in need of a reference work of this kind.

B. L.

DISEASES OF THE NOSE AND THROAT. For Practitioners and Students. By CHARLES J. IMPERATORI, M.D., F.A.C.S., and HERMAN J. BURMAN, M.D., Professor and Instructor respectively of Clinical Otolaryngology, NewYork Post-Graduate Medical School, Columbia University. Pp. 723; 480 illustrations, some in colors. Philadelphia: J. B. Lippincott Company, 1935. Price, $7.00.

THIS work contains a wealth of information briefly presented, which should be of great practical value to the student, practitioner and specialist. Methods of diagnosis and treatment of nose and throat conditions are tabulated. Considerable space is devoted to peroral endoscopy.

K. H.

RUSSELL A. HIBBS. Pioneer in Orthopedic Surgery, 1869–1932. By GEORGE M. GOODWIN. Pp. 136; illustrated. New York: Columbia University Press, 1935. Price, $2.00.

THE story of the work and life of a physician is always interesting. When the physician discussed has been responsible for an improvement in the treatment of the sick, such as surgical joint fusion, his story becomes inspiring.

Both physician and layman will find inspiration in this small biography of Russell Hibbs, the well-known pioneer in orthopedic surgery at Columbia, for he wrought both finely and well.

G. W.

PERSONAL AND COMMUNITY HEALTH. By CLAIR ELSMERE TURNER, M.A., DR.P.H., Professor of Biology and Public Health in the Massachusetts Institute of Technology, etc. Fourth edition. Pp. 680; 130 illustrations, 4 colored plates and 13 tables. St. Louis: The C. V. Mosby Company, 1935. Price, $3.00.

The new edition of this admirable book gives every indication of a thorough revision and much new work in hygiene and allied fields is to be found. Although written as a textbook for students of college grade, it contains much that every doctor of medicine should know and which is not to be found in the curricula of many of our medical schools.

Every educated person should know and understand all that this book contains, both from the point of view of caring for and developing personal health and from that of the good citizen. The chapter on Mental Hygiene is to be especially commended. The book is written in a clear, attractive style and with an excellent balance of commonsense and appreciation of the relative importance of a large body of knowledge. G. R.

MECHANICS OF NORMAL AND PATHOLOGICAL LOCOMOTION IN MAN. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor of Orthopedic Surgery, The State University of Iowa, Iowa City, Iowa. Pp. 424; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $8.00.

THIS text, a revised presentation of the author's lectures, is divided into two parts.

Part I, "General Mechanics of Locomotion," covers the history of mechanics of the locomotor system, the definition and scope of kinesiology and its relationship to allied sciences, the relation of the general laws of mechanics to human motion, the center of gravity and methods of determination, the physical properties of bone, the dynamics, electrophysical analysis and coördination of skeletal muscle action. The last chapter is devoted to a discussion on fatigue and recovery.

Part II deals with "Special Mechanics of Locomotion" as applied to the various joints, the spine, the pelvis, respiration and abdominal cavity. There are three chapters on the human gait covering normal and pathologic mechanics. In the last chapter on the rationalization or work in locomotion is discussed the calculation of external work, energy determination and optimum efficiency.

This book is well illustrated with photographs and drawings and contains a wealth of material on the subject which should be of practical value to the practitioner of medicine, teacher of physical education and scientific investigation. To realize its full value the book should be studied and not merely read. T. O.

THE HUMAN FOOT. Its Evolution, Physiology and Functional Disorders. By DUDLEY J. MORTON, Associate Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 244; 100 illustrations. New York: Columbia University Press, 1935. Price, $3.00.

AFTER reviewing his work on the evolution of the foot and man's posture, the author takes up the normal physiology of the foot and evaluates the importance of its various parts. Though far from complete, as the author emphasizes in his Preface, it is probably the best monograph in English dealing with the anatomy, physiology and pathology of the human foot. G. W.

APPARATUS AND TECHNIQUE FOR ROENTGENOGRAPHY OF THE CHEST. By CHARLES WEYL and S. REID WARREN, JR., Moore School of Electrical Engineering, University of Pennsylvania. Pp. 166; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $5.00.

THE authors of this volume state in their preface that in order to obtain optimum results in diagnostic roentgenography of the chest, it is essential to have a scientific working knowledge of the physical principles underlying the theory and practice of roentgenographic technique and practice. They have collected such data and knowledge and have presented it in a condensed and attractive form. It is true, they also state, that most roentgen-

ologists are forced by circumstances to spend so much of their time in the practice of their profession and in keeping abreast of medical development that it is impossible for them to make a thorough study of these principles. Up to the present time, all such information has been confined to isolated technical papers and brief references in textbooks emphasizing primarily the interpretative aspects of roentgenograms. The first chapter deals with a summary of the phenomena associated with the production of chest roentgenograms. The inherent inefficiency of the process and the conflicting requirements imposed upon the choice of technique are discussed. In the second chapter on roentgenographic apparatus, the portion describing in detail the advantages and disadvantages of each type of high voltage generator is especially useful to the roentgenologist. The actual roentgenographic technique, the practical application of the principles previously discussed, fills the third chapter. Methods of measurement and standardization of apparatus and technique are found in the fourth chapter. An appendix is added on elementary electrical theory for those who are not currently familiar with the basic principles involved in roentgenography. This book cannot be recommended too highly, not only because it contains material not previously published in book form which makes it valuable as a text as well as a reference book, but also because the technique is based on actual clinical investigations and experience, the result of investigations carried on for 10 years by the authors in the laboratories of the Moore School of Electrical Engineering, University of Pennsylvania, and in the Roentgen ray clinic of the Henry Phipps Institute by Dr. F. Maurice McPhedran. It is a book that should be included in the working library of every roentgenologist. R. B.

A Terminology of Operations of the University of Chicago Clinics. By Hilger Perry Jenkins, M.D. Pp. 99. Chicago: University of Chicago Press, 1935. Price, $1.00.

In the foreword the author expresses the difficulty often encountered in looking up operations of a certain type in hospital record rooms. The difficulty lies in the varied nomenclature which individual surgeons use for the same operation. The monograph was designed primarily to develop a terminology which could be used with facility as an operation index in any hospital. All synonymous terms have been grouped together, and the subdivision of a main operative term heading has been carried out in certain instances according to the differences in operative technique. The index is complete and was designed so as to be readily available. The work will prove to be very valuable in every hospital which includes surgical services. I. R.

International Clinics. Vol. IV. Forty-fifth Series, December, 1935. Edited by Louis Hamman, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 331; illustrated, also 2 colored plates. Philadelphia: J. B. Lippincott Company, 1935.

As usual, this number presents a well-distributed subject material by well-known medical and surgical authors. All parts of this country are represented, with one article from England. The papers on Idiopathic Steatorrhea and Hypocytic Leukemia, each with a colored plate, especially attracted this reader. How much better is the latter name than the absurdity of Aleukemic Leukemia! Good, old-fashioned clinical acumen appears in the opening article on Observation of the Tongue, while therapy is represented by 3 articles, empyema, peripheral arterial disease and bacterial vaccines (but for the last, Oh! how pessimistically!).

E. K.

CELSUS DE MEDICINA. (In Two Volumes.) Volume I. With an English translation by W. G. SPENCER, M.D. (LOND.), F.R.C.S. (ENG.). (The Loeb Classical Library.) Pp. 499. Cambridge: Harvard University Press, 1935. Price, $2.50.

OF the 60 odd Latin and almost 100 Greek works that have thus far achieved inclusion in this collection, only the 4 volumes of Hippocrates and Galen's "Natural Faculties" are medical in nature. Thus this volume is the first Latin work to be included in the series. From W. H. S. Jones' Introduction we learn, among the few items known about Celsus, that he probably lived at Narbonne and that this work was but the second of 6 of a large treatise covering agriculture, military arts, rhetoric, philosophy and jurisprudence. Several reasons are given for believing that Celsus was not a mere compiler but practised medicine himself. In addition to the historical summary in the Proemium and the celebrated cardinal signs of inflammation (p. 273), the reader will find much to convince him that Celsus had not the mediocre mind that Quintilian mentions. Like Jones' Hippocrates in this series, the handiness of the format promotes perusal and the parallel pages of Latin and English invite even the veriest tyro of a Latinist to sharpen his faculties on the clear forcible and flowing style of the Latin text. E. K.

THE RANGE OF HUMAN CAPACITIES. By DAVID WECHSLER, PH.D., Chief Psychologist, Psychiatric Division, Bellevue Hospital, New York City. Pp. 159; 11 figures and 22 tables. Baltimore: The Williams and Wilkins Company, 1935. Price, $2.50.

THE modest dimensions of this book are by no means a measure of its inspiration or of the author's achievements. He attains brevity and clearness by a fine hand in the management of his materials and by the excellence of his writing. The first five chapters are a well-written exposition of the problem of measurement and range of human capacities. Even for those less conversant with the intricacies of statistical method, the author succeeds in making clear the method of approach and the pitfalls of statistical logic. His proposal to establish human values in terms of pure numbers is an advance in making intelligible the study of personality, and this method reveals a rather surprising fact, that human capacity as expressed as ratios between extremes of ability have "strikingly recurrent values which fall roughly with the range of 1.2:1 to 1.5:1; in brief, indicating that human variability is relatively limited. The author's discussion of the limitations of analysis, and particularly of the theory of probability as related to measurement of human abilities, should invite wide reading. The remaining four chapters will interest the less mathematically minded reader because of the novel treatment of exceptions, particularly of deficiency and genius and because of the author's developed contention that, contrary to the current doctrine, human capacity has a tendency to reach its zenith in youth and almost steadily to decline from that point on with the advance of age. P. R.

THE PATIENT AND THE WEATHER. VOLUME I, PART I. THE FOOTPRINTS OF ASCLEPIUS. By WILLIAM F. PETERSEN, M.D., Department of Pathology and Bacteriology, University of Illinois College of Medicine, Chicago. Pp. 127, lithographed; 94 illustrations. Ann Arbor: Edwards Bros., Inc., 1935. Price, $3.75.

IT is proposed that this series shall consist of five or six volumes; their release in reverse order—III, II, and the present one—is rather confusing. The responsibility of other factors is admitted but the weather environ-

ment is regarded as a most important one. Complaint is made that we think too pathologically, that we "teach medicine as a science of death." And here one recalls what has elsewhere been said: "There are no diseases, only diseased persons."

In this portion of the thesis, the outstanding chapters are: Changing Restlessness of the Winds in America; Racial Differentiation; Disease, and consideration is here given to endocrine disturbances, anemias, cardiovascular renal disease, epilepsy, cancer, syphilis and acute infection. This most difficult subject is still in the research phase and the author merits praise for his diligence and intelligence in assembling the data in support of the argument he is advancing. An abundant bibliography is included, but it is a matter for regret that indices are lacking. N. Y.

NEW BOOKS.

Injury and Incapacity. With Special Reference to Industrial Insurance. By H. ERNEST GRIFFITHS, M.S. (LOND.), F.R.C.S., Surgeon, Albert Dock and Hertford County Hospitals; Consulting Surgeon, Wimbledon Hospital, etc. Pp. 270. Baltimore: William Wood & Co., 1935. Price, $5.00.

Teoria de Los Neoplasmas. By S. SANTAMARIA. Pp. 163; 13 illustrations. Madrid: J. Pueyo, Imp., 1935. (No price given.)

Anatomy of the Rat. By EUNICE CHACE GREENE, Vol. 27 of the Transactions of the American Philosophical Society, held at Philadelphia, for Promoting Useful Knowledge. Pp. 370; 338 illustrations, partly in color. Philadelphia: The American Philosophical Society, 1935. Price, $5.00.

Cold Spring Harbor Symposia on Quantitative Biology, Vol. III. Pp. 359; illustrated. Cold Spring Harbor, Long Island, N. Y.: The Biological Laboratory, 1935. Price, $3.75.

Bauerndoktor. By MENHOFERS FRANZEF. Pp. 184. München: Verlag der Ärztlichen Rundschau, 1936. Price, paper, Rm. 2.81; bound, Rm. 3.60.

Aus meinen Krankenblättern. Von der Arbeit eines Landarztes. By DR. AUGUST HEISLER, Sanatorium Luisenruhe und Kinderweide Königsfeld im Schwarzwald. Heft 47 of Sammlung diagnostisch-therapeutischer Abhandlungen für den Praktischen Arzt. Pp. 68. München: Verlag der Ärztlichen Rundschau, 1936. Price, paper, Rm. 1.58; bound, Rm. 2.25.

NEW EDITIONS.

Demonstrations of Physical Signs in Clinical Surgery. By HAMILTON BAILEY, F.R.C.S. (ENG.), Surgeon, Royal Northern Hospital, London; Surgeon and Urologist, Essex County Council; Consulting Surgeon, Clacton Hospital, etc. Pp. 287; 341 illustrations, many in colors. Fifth edition, revised. Baltimore: William Wood & Co., 1935. Price, $6.50.

The Radiology of Bones and Joints. By JAMES F. BRAILSFORD, M.D. (B'HAM.), M.R.C.S. (ENG.), Hunterian Professor, Royal College of Surgeons, England, 1934–1935; Radiological Demonstrator in Living Anatomy, The University of Birmingham, etc. Pp. 571; 340 illustrations. Second edition. Baltimore: William Wood & Co., 1935. Price, $9.00.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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STUDIES ON INFLUENZA.

Pandemic Influenza. Pandemic influenza, the severe, highly contagious form of influenza, may reasonably be expected to return if we may rely upon epidemiological history. This review of progress will be an outline of what has been accomplished towards the solution of the many problems of influenza during the last 4 or 5 years, particularly those concerning its etiology. Laidlaw has roughly estimated that in the last great pandemic of 1918–1919 500 million persons were attacked and 15 million lives were lost. With such a tragic possibility before us it may be well to consider whether the medical profession is prepared to focus its attention on specific problems demanding specific answers or whether it will be again confused in a maelstrom of phenomena with its energies scattered and ineffective. The actual difficulties must be clearly recognized and the limitations of what may be hoped for defined.

Definition of Influenza. There is no agreement among clinicians as to just what is meant by influenza and this constitutes today the greatest difficulty in the scientific search for etiological agents. During the pandemic it was generally accepted that we were dealing with a specific disease *en masse*, although only when statistics are available does the individual physician realize that an epidemic is present, and there follows a strong tendency to be swept along by a single diagnosis. The severity of the respiratory symptoms, the high contagiousness, the frequency of a peculiar and often fatal pneumonia associated with cyanosis, the evidence for lack of bodily defense as seen in the common occurrence of a leukopenia, the muscular and other aches and pains, and the early asthenia so often prolonged into convalescence, all these make up the syndrome called influenza. However, the individual cases are widely different from each other and from the etiological side this

is immensely confusing. Many consider that the mild and practically non-fatal influenza should be differentiated from influenza with pneumonia (Gundel, 1933), and that the cases in a pandemic have not the same etiology as the sporadic or smaller epidemic cases (Selter, 1933). Still others find it difficult to separate individual cases of influenza from the so-called "cold" diseases (Meyer, 1933). Berger *et al.* (1934) regard the smaller epidemics as only quantitatively, not qualitatively, different from the pandemic of 1918, and that it is the same disease entity, the characteristic leukopenia developing as the disease becomes more contagious. Laidlaw believed many sporadic cases of influenza may not be of the same character as those of the pandemic outbreaks and thought it more honest to diagnose these as P.U.O. (Pyrexia Unknown Origin). Even the contagious common cold with fever cannot always be sharply separated from influenza and although an exact diagnosis would seem to be the crux of the problem in etiologic studies, yet it must be recognized that at present this is impossible, and this fact must be considered in interpreting the results of experimental work. If we accept the familiar 3-day fever to be the same disease as epidemic influenza, and this latter the same as the pandemic type of 1890 and 1918, we certainly have a heterogeneous lot of signs and symptoms of different values in diagnoses and probably depending upon a variety of etiologic factors.

Whatever may be the etiologic contagious agent in influenza, there is no doubt that it increases in virulence and rapidity of spread just preceding and during the beginning of an epidemic and then gradually grows less and less active until in interepidemic times it is relatively innocuous. The epidemiologist demands, before an agent can be accepted as of etiologic importance, that the cycle of its existence be explained.

The condition of immunity in the population as a whole is variable and the individual with a reduced immunity to any agent may permit this agent to begin a process of human passage from person to person with, if enough susceptibles are available, a gradual increase in the contagiousness and later in the virulence of the agent. This theoretical consideration is difficult to study, but some evidence of such an occurrence is desirable in any infectious theory of influenza.

The proof that a particular infectious agent is the primary causative factor in such a disease as influenza is particularly difficult to obtain. The following are some of the requirements that such an agent should fulfill: 1, It should be shown to be in a fully virulent state when isolated from the acute disease and be relatively abundant in the lesions but not necessarily in all the involved tissues; 2, there should be evidence that the agent readily spreads from person to person; 3, the lesions induced in man or animals should closely resemble those found in the natural disease and should not be produced by other agents; 4, the agent should exhibit toxic qualities so that the evident toxicity of influenza may be explained; 5, reservoirs or carriers of the agent, not necessarily nor probably in the fully virulent form nor in large amounts, should be discovered to account for its survival during interepidemic times; 6, the agent should induce specific serologic changes in those having or convalescent from the disease, such antibodies should be

absent in the susceptible and present in the resistant, and all grades of the disease should be accounted for by the relative balance between the virulence of the agent and the immunity in the host; 7, if the agent is only part of a synergistic combination the characteristics of each agent individually must be clearly defined as well as the combined effects.

Hemophilus Influenzæ as a Primary or as an Essential Secondary Agent in Epidemic Influenza. There are widely divergent opinions on the relationship of H. influenzæ to the disease influenza. While the evidence for the virus theory has been accumulating, there has been a tendency to disregard the newer studies in favor of Pfeiffer's bacillus. So much has been learned about this bacillus since the pandemic of 1918–1919 that many of the adverse criticisms have not as much weight today as they formerly had. There are still many prominent bacteriologists who support the etiologic significance of H. influenzæ or who realize that the evidence against it must be reconsidered in the light of present-day knowledge. I shall, therefore, briefly outline certain evidence for and against the etiologic significance of the influenza bacillus.

The finding of influenza bacilli in normal persons or in those suffering from diseases other than influenza is perhaps the strongest argument against its importance. However, the evidence is not very great that H. influenzæ is present as the predominant organism or even in large numbers in normal persons. Thompson and Thompson (1935) have never found it abundant in the normal. It is well established, however, that the hemoglobinophilic bacteria do make up part of the so-called "normal" flora of man. Furthermore, other bacteria of accepted specific pathogenicity are known to be found in normal persons or in other diseases.

Virulence of H. Influenzæ. Our knowledge of the virulence of this bacterium has grown very slowly and is still far from being complete. The early work of Hudson (1922), who used intraperitoneal injections in white mice showed that Pfeiffer's bacillus was often pathogenic and readily invaded the blood stream and that the strains isolated during influenza epidemics at military camps were more pathogenic than strains from other sources. Cultures mixed with pneumococcus were definitely more invasive. Three or four passages through white mice did not appreciably increase its virulence. In 1924 he noted that freshly isolated strains of H. influenzæ were increased in virulence when mixed with recently isolated strains of hemolytic streptococci or with stock strains of Type I pneumococcus, and he showed further that the Pfeiffer bacillus if injected first, acted as a sensitizer of the host to hemolytic streptococci but that the reverse did not occur.

More recent work has clearly shown that H. influenzæ is a most variable microörganism and has established certain criteria for differentiating typical and atypical forms which were partly distinguished on morphologic grounds by earlier workers (Pfeiffer and others), the atypical being often named para-influenzæ. This differentiation was uncertain and not generally accepted as of significant value until Pittman (1931), using non-hemolytic strains specifically requiring the X and V factors, divided the cultures into well defined typical and

atypical types. The typical cultures showed coccobacillary morphology and capsules yielding a specific polysaccharid, grew in smooth colonies and were called the smooth or S type. The atypical tended to grow in longer bacillary up to thread forms, had no capsules and grew in relatively rough colonies and were considered as R forms. The colony differentiation required a clear blood medium such as Levinthal agar. Kun and Fenyvessy (1932) described similar forms also using non-hemolytic strains requiring X and V factors and believed that the Pfeiffer bacillus varied through a series of continuous and reversible changes, the particular form encountered depending on the biologic conditions of the host at the time. They were able to bring about changes into all the different forms by experiments on animals. The morphology did not always completely correspond to the colony type. The typical coccobacillary form was found in early disease and caused death in white rats and mice after intraperitoneal injections. The atypical occurred later in the disease and never caused death in animals. The virulence could be raised by animal passage. Kairies (1932) studied particularly the pathogenicity of H. influenzæ in mice and believed that the injury after intraperitoneal injection was due to toxin and that true pathogenicity was problematic. Mixtures of streptococci and Pfeiffer bacilli were more active in causing death in mice than was either alone. He advocated the use of Levinthal agar and inoculation of mice for the isolation of H. influenzæ. Dochez, Mills and Kneeland (1932) found in chimpanzees which developed common colds after inoculation with a virus preparation, that the H. influenzæ in their respiratory tract was transformed from the non-specific R form to the specific S form, and that a reversal followed the return to health.

Pittman (1933) produced in a horse a type specific antiserum with Type B bacteria (a form often occurring in meningitis cases) which prevented the blood stream invasion of H. influenzæ after intraperitoneal injection of mice and rabbits but did not affect the toxicity. Prausnitz (1933) suggested that strains of low virulence are raised in virulence by growing in the respiratory tract of sensitive persons. Kühn (1934) stressed the evidence that H. influenzæ is pathogenic in inflammatory and purulent lesions quite independent of influenza. Hoyle (1934)[1] followed the incidence of the typical and atypical strains in 17 persons from September to March with fortnightly cultures unless evidence of infection occurred when more frequent cultures were made. He used mouse inoculation, heated blood agar, blood broth, penicillin agar (with which Fleming and MacLean (1930) had successfully cultured H. influenzæ of varying morphology from all of 36 normal persons), and determined the X and V factor requirements of all strains and their ability to produce indol. The typical or S cultures corresponding to those described above, were isolated by the mouse method almost always, invading the blood in 70% in mixed cultures, but only in 30% when pure. They were practically never found in normal respiratory tracts but coincided very closely or preceded the onset of a coryza. Of the 32 fully virulent strains 26 were from those with acute coryza, influenza or sore throat and 4 with chronic catarrh, the others were apparently from temporary carriers. A number of the acute coryza attacks were associated with an increase in pneumo-

cocci. Capsules could not be demonstrated on their virulent strains of H. influenzæ. The atypical or R cultures were never isolated by the mouse method; even when numerous colonies appeared on the penicillin agar, they were all non-pathogenic for mice, *i. e.*, did not invade the blood stream, although toxic deaths occurred in some and they were the only forms isolated in the disease-free month of September. Isabolinski and Stratanowitsch (1934–35), who were former advocates of a diplo-streptococcic etiology for influenza, had the opportunity of studying 15 very early cases and isolated H. influenzæ from all of these. Cultures inoculated into the nose of rabbits produced a purulent discharge and the serum of these animals after 15 days showed agglutinins, and complement-fixing antibodies in 2 of 3 rabbits, while in 1 rabbit there were lung lesions. Hoyle (1934)[2] was able to raise the virulence of strains of H. influenzæ provided the initial virulence was such that 0.5 cc. killed a mouse on intraperitoneal injection. He did this by intrapleural inoculation in young rabbits and a series of rabbit passages until the virulence was such that 0.05 cc. killed a mouse. The strain could be kept by this technique at full virulence, the morphology was of the coccobacillary type, the colonies were watery and intrapleural inoculation induced in young rabbits a typical bronchopneumonia which he could not produce by similar treatment with pneumococci of high or low virulence, hemolytic streptococci or staphylococci. However, B. coli of suitable virulence gave a similar result. Although Hoyle does not say that the suitable B. coli cultures were indol producers, it is an interesting possibility since indol is a rather toxic substance. In an earlier report Hoyle (1934)[1] said that 18 of 28 cultures of H. influenzæ of the typical form were indol producers and that all the 27 atypical were indol negative. Rosher (1931), in a study of strains of H. influenzæ, all requiring both X and V factors, found that their pathogenicity in the peritoneal cavity of mice was increased if the X and V factors were injected along with the bacilli. Of 45 indol positive strains, 26% killed mice on ordinary injections and 71% did so when reinforced as above. Of 45 indol negative strains none killed by ordinary injection and only 6% when reinforced. Huntington (1935) studied the forms of H. influenzæ in certain diseases of children and proposed that the watery fluorescent form be called M or mucoid, the ordinary form S or smooth and that R be retained for the rough form described by Holster (1931) and Scott (1929). Since the R form is only an extreme dissociant obtained after prolonged cultivation on media and is not encountered on primary isolations or even in early transfers, the reviewer believes it is unwise to do more at present than accept the fact that H. influenzæ is extremely unstable in its morphologic and growth forms but that attempts should be made to correlate the type forms at the time of isolation with the presence or absence of animal pathogenicity and of disease processes in the patients. I can, therefore, only say that Huntington did not find H. influenzæ in the nose of children in the absence of respiratory disease, that S(M) strains were sometimes obtained on mouse culture only and that his evidence does not show a correlation between the occurrence of S(M) forms (apparently usually determined on subculture) and the type and severity of the disease. Hoyle (1934)[2], with the strains of H. influenzæ

of raised and stable virulence referred to above, attempted to infect rabbits and guinea pigs with intratracheal inoculations of 0.5 cc. pleural fluid containing the bacilli, and obtained hemorrhagic edema of the lungs but could not recover the bacilli from the site of the lesions. In a few of the controls inoculated with media, however, lesions were produced, some of which were as severe as in those receiving the bacilli. A massive dose of 3 to 4 cc. gave a confluent pneumonia and the bacilli were recovered from the diseased lung. The author warned against neglecting the traumatic effect of such inoculations and particularly stressed the toxic effect. Toxic bacilli can without doubt cause marked lesions and the bacilli may be destroyed at the site of the reaction.

The presence of H. influenzæ in the upper respiratory tract of animals used for experiments is important. Dochez, Shibley and Mills (1930) found Pfeiffer bacillus in 92% of the throat cultures and 13% of the nasal cultures of normal apes as contrasted with 47% and 0% from normal man. They also reported the occurrence in a chimpanzee of a spontaneous cold apparently contracted from the keeper which was followed by a fatal bronchopneumonia from which hemolytic streptococci, Pfeiffer bacillus and other bacteria were recovered. These findings, together with the later report of 1932, already referred to, showing the transformation of R to S forms during the course of a common cold, suggests the great difficulty in the interpretation of results after experimental injections under such circumstances. Kairies (1934) described a sporadic influenza epizoötic among fitchets with the recovery from them of H. influenzæ. With material from the lungs of one of these animals a ferret (with throat cultures negative for H. influenzæ for a week) was inoculated in nose, throat and eye and developed a disease with conjunctivitis, catarrh and the diphasic temperature changes described for the virus disease by Smith, Andrewes and Laidlaw (1933). H. influenzæ was repeatedly isolated from this animal. A contact ferret previously free from H. influenzæ, gave positive throat cultures after 3 days and became ill in 6 days. Two fitchets which remained alive became bacillus carriers. The animal caretaker was a carrier since 1918 and his 10-year-old son with chronic pharyngeal catarrh yielded cultures of H. influenzæ. A student working with the fitchets also developed influenza apparently from them, but before the bacteriologic study had started. Kairies also produced the disease in ferrets by repeated spraying with the sputum of a carrier and by a single spraying with the sputum of an acute sporadic case of influenza. In 1935, Kairies reported an outbreak of sporadic cases of influenza in ferrets which occurred in the winters of 1933–34 and 1934–35 with symptoms like the virus disease and H. influenzæ was present in all the diseased animals. The spread of the bacilli from symptomless carriers to other ferrets was also shown to occur. He described certain differences between the bacillus of ferrets which he named Bacterium influenzæ putoriorum multiforme, and the human strains of Pfeiffer bacillus based on colony and agglutination studies and the marked pleomorphism of the former, but it would seem that similar differences can be found among strains of human origin. The H. influenzæ of swine will be considered under the discussion of the virus of swine influenza.

In 1934 Shope used ether anesthesia primarily to suppress the sneeze reflex of his ferrets before intranasal inoculation with swine influenza virus and thus produced a disease more severe clinically and more extensive pathologically than had been previously obtained by those not using an anesthetic. As a result of this, light ether anesthesia has become more or less generally used for all nasal instillations of ferrets, white mice and other animals, and this has opened up a new technique widely applicable to the study of infections of the respiratory tract, especially for the experimental production of pneumonia. I will here consider the use of ether in the study of bacterial infections, but should point out that very little has been done to determine the exact mode of action of the ether. Neufeld and Kuhn (1935) applied the method in their experiments with pneumococci in white mice and obtained a disease picture entirely different from any previously obtained by other methods designed to reduce the resistance before intranasal instillation. This disease picture was much closer to human pulmonary inflammation than any previously obtained. They also showed that ether markedly increased the virulent action of other microörganisms as well as the production of pneumonia after intranasal inoculation, but with direct injections into the lung the ether had not so evident an effect. In tests on guinea pigs infected with pneumococcus the ether gave no such result. They showed by the use of India ink instilled into the nose of anesthetized mice and guinea pigs that in the mice the India ink spreads rapidly into the bronchi and appeared to act like a bloodless intratracheal injection, but in the guinea pig this intensive pulmonary infiltration failed and only small black foci appeared at the lung hilus. This is not the only factor, however, since intrapulmonary injections without ether do not give the same picture or results. In a later study Neufeld and Collier (1935) used this technique for producing pneumonia in mice in a study of various therapeutic preparations. Hoyle (1935) tried to repeat the virus work of Andrewes, Laidlaw and Smith (1934), who had confirmed Shope's results with ether, but he did not agree that the lung lesions induced by the virus in mice were specific. He considered them examples of aspiration pneumonia and was able to produce similar lesions, although more severe, by using pathogenic bacteria and ether anesthesia. Among the bacteria thus successfully used was H. influenzæ which, when fully virulent, killed 21 out of 30 mice, but when less virulent did not kill any of 12 inoculated mice. Filtrates from the lungs of such mice did not carry on the disease, so that he did not suggest that a virus can be so obtained.

There is needed, in order to explain many of the results with this new technique, a thorough comparative study of the finer anatomy and physiology of the respiratory tract of mice, ferrets, swine, man and other animals. The differences in the patterns of ciliary movements in man and monkey on the one hand and the mouse, rat and other animals on the other are described by Lucas and Douglas; but it is only suggestive of the problem before us. St. Clair Thomson's (1935) lecture on "The Defences of the Air Passages" is well worth reading in this connection.

Just a word may be added about the serologic evidence in favor of H. influenzæ. The numerous heterogeneous types as indicated by the

results of agglutination tests are no longer significant because of the antigenic variability of H. influenzæ. Gundel (1934) considered the agglutination test unsuitable to indicate the state of immunity in man and advocated the complement-fixation test, great importance being given to having the proper antigen prepared in the same way as that used in pertussis (Gundel and Schülter). Pittman and Goodner (1935) prepared antisera against well studied strains of H. influenzæ in the horse and the rabbit. Both these sera gave good results by agglutination (of the type specific strains) and precipitin reaction (with the type specific polysaccharid). The complement-fixation test gave positive results with the rabbit antiserum but negative results with the horse antiserum when the polysaccharid was used as the antigen. However, if bacilli (either R or S) are used as antigen, then the rabbit serum gave a complement fixation with all strains of Type B tested and the horse serum was positive with all but one strain. Both antisera contained both rough and smooth antibodies; but if the capsule were well developed as in the above negative strain, they believed the rough antigen was covered and the horse serum failing to fix complement with the polysaccharid could not reach the rough antigen, and the result was negative. The fact that one strain had a more stable capsule than the others is of interest in considering its possible effect on virulence.

If another pandemic of influenza should occur, it would be advisable in order to have the necessary facts in favor of or against the Pfeiffer bacillus to determine the following: 1, The presence of H. influenzæ of the non-hemolytic type and requiring both the X and V factors, in various stages in the onset and course of the disease, and if possible preceding the onset. To do so cultures should be obtained particularly from the nose, throat, sputum, and in pneumonia possibly by puncture from the lung. The technique must include a clear blood agar such as Levinthal agar, and the direct injection of mice in order to determine the form of the bacillus at the time of isolation both as to type of colony, morphology of the bacilli and the relative ease of emulsifying in broth or saline; 2, the pathogenicity of strains by intraperitoneal injection of mice with the primary mixed material as well as with pure cultures and with mixtures of H. influenzæ and the other bacteria present. This would include lethal power, invasion of the blood and survival of the bacilli in the peritoneal cavity; 3, indol production by the strains isolated which can be done from fluid media or by the oxalic acid paper technique over a blood agar slant; 4, the complement-fixing antibodies in the patient's serum using suitable strains of H. influenzæ to identify serologic antibodies against both the type specific polysaccharid of the smooth form or the species specific substances of the "capsule" free form. Agglutination tests may also be useful in certain cases and the facts concerning them should be increased; 5, the relationship of these results to the simultaneous demonstration of a virus-like substance in the filtrates of the patient's secretions.

A Filterable Virus in the Etiology of Influenza. Since most recent writers have reviewed the earlier work which suggested that a filterable virus might be a significant agent in influenza, I need not do so. Dochez and his associates studied filtrates from persons either with the common cold or with influenza and used a long series of human volunteers and

a few chimpanzees as experimental animals. Many of the responses to the intranasal inoculation with supposedly influenza virus closely resembled common cold of varying severity. Cultures of these filtrates in embryonic tissue gave similar results, but all these painstaking experiments lacked in decisiveness, perhaps because man is a most unsatisfactory animal to control.

The virus theory was revivified in 1931 with the brilliant series of articles by Shope on the etiology of swine influenza—"brilliant" being the word applied to this work in nearly every discussion on influenza since. The story of swine influenza has become well known. Briefly, it is that a disease appeared in 1918 among the swine in eastern Iowa which had so many points of resemblance to the pandemic of human influenza that Dr. J. S. Koen named it swine influenza. When the disease breaks out all the swine in the herd become infected in the early autumn and early winter epizoötics, but the mortality is only about 1% to 4%. Shope first showed that the disease could be transmitted by intranasal inoculation of materials from the respiratory tract of sick swine to healthy swine at Princeton, far distant from the locality in which seasonal epizoötics have continued to appear, there being no immune swine and no such disease at or about Princeton. He next proved that H. influenzæ, always present in the sick animals, did not by itself induce the disease when freshly isolated and presumably fully virulent cultures were used. He then tested filtrates of the contagious materials and found that bacterial-free filtrates produced a mild disease in swine, which he called the filtrate disease, but which had not many of the important characteristics of the epizoötic disease itself. The typical epizoötic disease, however, regularly followed the combined inoculation of both filtrate and bacilli. In 1932 Shope showed not only that immunity was conferred to swine by the natural disease and by a single intramuscular injection of the virus—the virus having shown no other demonstrable effect by any other route than the respiratory tract—but also that the bacillus itself produced no immunity. Köbe, in 1933, reported finding a similar virus from a disease of suckling pigs on the island of Reims in Germany which was quite different from the swine pest virus, was spread by contact, required the presence of H. influenzæ to produce the full pneumonic disease and, although it only occurred in young pigs, was probably identical with the virus of Shope. In 1934 Shope's important studies on contagion were reported, in which he showed that three types of infection could occur. 1, Full contagiousness in which both virus and bacillus were transferred by pen contact from the sick to the well; 2, partial contagiousness in which only the virus was transferred and resulted in the mild filtrate disease; 3, the establishment of carriers of H. influenzæ by the disappearance of the virus. In these last two types either the transfer of the bacilli or the virus brought back the full contagiousness of the complex. Following the report of Smith, Andrewes and Laidlaw (1933) on a disease in ferrets induced by filtrates from cases of human influenza, Shope, in 1934, anesthetized ferrets with ether before inoculation and was able to produce a more severe pulmonary disease in these animals with the swine virus alone, the bacteria not being an essential component. He thought that the effects of the ether were to favor the establishment of

the virus, to permit the giving of a larger dose because of the inhibition of the sneeze reflex and to make possible a deeper introduction of the virus. Although he believed that the method of the English workers came closer to the natural infection, nevertheless the fact that the disease produced by the use of ether was more definite, constant and easily recognized made it of value in such experiments. In 1935 Shope confirmed the results of Andrewes, Laidlaw and Smith (1934) and Francis (1934) concerning the transfer of the swine virus to white mice from infected ferrets, and was able to infect mice directly without ferret passage with one of two strains of the field virus of swine influenza, while with the other 2 or 3 mouse passages were needed. In the mouse disease he found no evidence that any significant rôle was played by the bacteria, fatal pneumonias being produced by pure virus infections. After mouse passage the virus remained equally infective for either swine or ferrets, that is, it was a stable virus. The mouse is, therefore, a useful animal for studying the pure virus disease. Most of the comparative work on the human and swine influenza viruses indicates that they are closely related if not identical, the swine virus, however, seeming to be both more stable and more virulent.

The new exciting investigation of human influenza virus began with the preliminary report of Smith, Andrewes and Laidlaw in 1933. These workers, stimulated by the work of Shope and the success of Dunkin and Laidlaw (1926) in discovering the virus of dog distemper by ferret inoculation, used this animal for the study of filtrates from the throat washings of human influenza patients. Intranasal inoculation was followed after about 48 hours by a non-fatal inflammatory disease of the respiratory tract with a diphasic type of temperature response. They were able to carry on the disease picture by inoculating preparations of the turbinates of the ill ferrets into the nose of new animals. The active substance was only recovered from the respiratory tract, neither lymph glands, spleen or blood being ever infective and the respiratory was the only route by which the typical response could be obtained. Contact spread of the disease from ill to well ferrets was mentioned as having frequently occurred but no details of this significant observation were given. The ferrets after recovery from the febrile disease were found to be resistant and the virus when mixed with their serums and inoculated into the nose of susceptible animals no longer induced the typical reaction. Normal ferret serum was said to have had no effect but the number of these tested was not given. Human sera were variable but usually neutralized the virus; for example, 10 human sera of persons recovered from influenza at first neutralized, but on retesting 2 of these failed; 3 sera from cases with no history of influenza failed in 2 instances and was able in 1 to neutralize the virus. The materials studied were the nasopharyngeal washings, often but not always filtered, from: 8 cases diagnosed as influenza, the reaction in ferrets being produced by 5 of these (62.5%); 4 cases without influenza (2 of these being recovered cases from whom the two viruses W. S. and B. W. had been obtained) which were negative in ferrets; and the nasal discharge of a man with a common cold which was also negative. They were also able to induce the typical ferret disease by the swine influenza virus obtained from Shope but found the influenza bacillus did not modify the disease produced in ferrets.

Kairies, as previously mentioned, reported a disease in ferrets of the same type as that described by the English workers which was transmissible from infected fitchets, occurred as a sporadic outbreak in his ferrets and could be transmitted to healthy animals by spraying with materials from a human carrier of influenza bacillus and from a patient with influenza. In all these influenza bacilli were found and were considered etiologically responsible. Kairies (1934) also experimented with a Shope virus preparation (dried lung substance containing a delicate streptococcus) and was successful in inducing this type of disease with the virus and influenza bacilli together and with the virus (containing streptococci) alone. Similar results were obtained with the human influenza virus preparations of dried nasal turbinates (obtained from Andrewes) and from which he grew streptococci, some ferrets, however, becoming ill after the virus alone but not severely so. Glycerinated (Köbe and Shope) virus free from bacteria gave less certain results. He laid particular stress on these non-hemolytic, very small streptococci as of symbiotic importance in assisting the influenza bacillus, having found them in all three preparations of virus and in a number of supposedly pure cultures of influenza bacillus, some of them on media for years, and believed it was significant as an optimal symbiont for the influenza bacillus. He believed that the transfer of human influenza material to ferrets induced in them the influenza peculiar to these animals.

In 1934 Andrewes, Laidlaw and Smith confirmed the results obtained by Shope with ether in ferrets and also obtained similar lung lesions without ether by direct inoculation into the lung. They further added a valuable technical method to the virus study by showing that white mice could be infected with these viruses. Swine influenza virus, after many passages through ferrets and a series of passages through mice, at first directly into the lung but later *via* the nose, became adapted to the mouse so that a high percentage became infected after nasal instillation. The human virus W. S. (obtained originally from the throat of Wilson Smith during an attack of influenza) was similarly adapted from the ferret to the mouse. Although ether is not necessary to produce the lung lesions these are always more severe when it is used. The culture media used in the bacteriologic control of these studies (plain agar, serum agar and blood agar) were not particularly suitable to discover the possible presence of influenza bacilli in any of these lesions. Filtrates from the lungs of these mice, however, produced the disease in a very high percentage of inoculated mice.

The mouse thus became a useful animal in the study of these viruses and particularly for testing the neutralization of virus preparations by antiserum. The technique used for this latter purpose was to mix the virus preparations with the serum to be tested and to inoculate the mixture intranasally into mice. The controls were practically always the virus correspondingly diluted with saline. The serum from hyperimmunized horses taken before immunization was said to have had no effect, but whether it was tested while fresh or months later when the other tests were made was not stated, nor are any details given of this important test. If all of the serum treated mice had been protected against lung lesions and all those untreated had shown such lesions,

this absence of adequate controls might not have seemed so significant, but until more exact information is available about the mechanisms which determine the distribution of materials put in the nasal cavity and about the effect of ether on these it may logically be deduced that serum may change the local conditions and favor the passage of such mixtures to the esophagus rather than to the trachea. The results of Sabin (1935), in his study of the mechanism of immunity to filterable viruses, would indicate that such viruses are not inactivated *in vitro* by antisera. He reported that the virus of pseudorabies, which was equally infective in the guinea pig by either the cerebral or nasal route, was apparently inactivated by a very much smaller amount of antiserum if the mixture were slowly dropped into the nares than if it were injected into the brain. Francis and Magill (1935),[1] in a study of Rift Valley fever virus, reported that when the virus was mixed with immune serum and given by the intraperitoneal route no evidence of infection was observed, but when immune serum and virus was administered by the intranasal route there may be little detectable difference between the protective effects of immune and normal serum. Neufeld and Kuhn (1935), as previously mentioned, showed that under ether mice permit carbon instilled into the nose to be more widely distributed than do guinea pigs.

Francis, in 1934, recovered viruses from the glycerinated sputums of 3 cases of epidemic influenza sent to New York from Puerto Rico. The sputums, washed and emulsified in Locke's solution, were inoculated intranasally into anesthetized ferrets and produced the febrile ferret disease which, after a series of passages using Berkefeld filtrates or unfiltered lung suspensions, resulted in definite lung lesions. Of particular interest was the development of influenza by one of the laboratory workers (S. S.) and the transmission by his bacteria-free nasopharyngeal washings of a febrile disease to ferrets but without pulmonary consolidation. As with the English workers, there were no deaths among any of his infected ferrets. He also was able to transmit the disease to white mice, certain breeds being particularly sensitive, but the lung lesions only developed after passage.

Hoyle (1935) studied the disease produced in anesthetized white mice after intranasal inoculation of certain of these viruses obtained from Andrewes as well as with pathogenic bacteria. The results with the latter are referred to above. He found that the swine influenza virus of Shope, received as desiccated mouse lung, caused lung lesions and on passage these as well as the fatalities among the mice markedly increased. Filtration resulted in a considerable loss in potency, but severe lesions from which no bacteria could be grown were produced with bacteria-free filtrates. Contact transmission of the disease by exposing large numbers of mice to those fatally ill was completely negative. Control mice given sterile broth and normal mouse lung preparations showed no pulmonary lesions. The results with the human viruses were less successful. The B. W. virus (desiccated ferret nasal mucosa) gave an occasional bacteria-free lung lesion in mice. Chamberland L2 filtrates produced at first no lesions, but after passage, using unfiltered preparations, a rise in virulence occurred simultaneously with the appearance of a Gram-negative coccobacillus in the lesions

and preparations. These bacilli passed a Seitz filter. Bacteria-free filtrates gave either no lesions or very tiny non-transmissible ones. The W. S. virus (desiccated mouse lung containing Gram-negative bacilli) gave a variable number of lesions but these all contained small numbers of the small coccobacillus, and on passage this bacillus and the lesions increased. Bacteria-free Seitz filtrates were negative. A 50% glycerol preparation removed the bacteria and this bacteria-free "virus" produced fatal lesions. Hoyle attempted to isolate viruses by direct inoculation with human material from: 1, 5 cases of contagious acute pharyngitis and tracheitis—the unfiltered washings contained Friedländer bacilli resistant to glycerol and no evidence of a virus could be obtained; 2, a case of severe sore throat with negative results; 3, a case of typical acute coryza, washings from which gave transmissible pulmonary lesions with no demonstrable bacteria for several passages, and when bacteria did appear they were readily removed by glycerol without affecting the potency of the preparations. Seitz filtrates were very indefinite. Hoyle believed all these lung lesions induced by virus are examples of aspiration pneumonia, as also are those induced by bacteria and that these cannot be considered as representing a specific illness comparable to human influenza. He also considered the apparently non-bacterial agent he obtained from coryza as similar to the B. W. and W. S. human viruses. He concluded that conditions possessing the epidemic features and high infectivity of human influenza have not been produced in mice by these viruses nor has it been demonstrated that these viruses can be isolated from every case of influenza nor that they are absent from other respiratory diseases.

Francis (1935)[1] believed that at least one of the interpandemic diseases called influenza is causally related to a filterable virus and can be transmitted experimentally to mice and ferrets and that this fact will help to differentiate influenza from other respiratory diseases. In addition to the virus strains from Puerto Rico he has obtained similar viruses from mild epidemics of influenza in New York and Philadelphia and from another assistant in the laboratory. The disease he induced in ferrets was at first only the mild diphasic, febrile one, but after a few passages lung lesions resulted and the disease was more severe. He was unable to transfer the disease directly to mice from man. Francis (1935)[2] further showed that the sera of ferrets, recovered from infection after P. R. 5, P. R. 8 and Philadelphia virus reactions, as well as Andrewes' horse serum (prepared with British strains of virus), were able to neutralize the effect of both the P. R. 8 and the Philadelphia virus when mixed with these viruses and injected into the nose of mice. Normal ferret serum, normal horse serum and convalescent swine influenza serum from Shope (all presumably fresh) had no inhibiting effect in that all of these controls developed well marked lung lesions. These results are very much more definite than any others so far reported.

Laidlaw, Smith, Andrewes and Dunkin, in 1935, gave a detailed report of their experiments with three sera from horses immunized with the turbinates or lungs of ferrets infected after human or swine virus inoculations. There were present in these sera precipitins for normal ferret serum, hemolysins for ferret cells and complement fixing antibodies with ferret lung emulsions. In all those tests which are

recorded in detail the controls were as above only virus in saline, although they say the normal sera did not neutralize the virus. Mice were used in nearly all the studies because the virus does not spread from animal to animal in this species and larger numbers can be used. The W. S. was the human virus used in most of the tests. They noted that passage virus ultimately leads to lung abscess in some mice and that Gram-negative, bipolar bacilli were sometimes found. The virus varied considerably in different tests so that often some of the controls survived or showed minimal lesions. In the experiments with passive immunity by intraperitoneal injection of serum the control animals were untreated. The tests were rather irregular but the intraperitoneal injection of antiserum 24 hours after the nasal inoculation of virus seemed to be beneficial. Various fractions of the antiserum, particularly pseudoglobulins were tested. They noted that the mice injected with large doses of horse serum often became ill at once, that the concentrated pseudoglobulin seemed more toxic and they found this was caused by agglutinins for mouse red blood cells in the horse serum there being more of these in the concentrated serum. This temporary reaction after intraperitoneal injection must be considered as affecting the resistance in the respiratory mucosa, perhaps by reflex action, and may very well be a factor in preventing the establishment of the virus, although the authors considered it an undesirable side action of the antiserum. Normal horse serum giving this same reaction should have been, but was not, used in the controls and, failing such controls, the results cannot be fully accepted as due to pure antibody action. The lesions found in the mice which received serum 24, 48 and 72 hours after the virus and lived are considered as due to the effect of the virus before it was neutralized, but no suggestion is made that the serum itself may have contributed to these lesions. The results using a large number of mice in each experiment are similar. Of 25 mice given virus alone, 5 lived (20%); of 24 given virus by nose and 24 hours after serum intravenously or intraperitoneally, 16 lived (66.6%), and of 25 given serum 48 hours after the virus, 15 lived (60%). They said that a pseudoglobulin fraction made from normal horse serum had no curative effect but they did not say that this serum had or had not agglutinins nor what its source was. The authors are convinced that certain epidemics of influenza are caused primarily by a virus infection.

Smith, Andrewes and Laidlaw (1935) experimented on methods for immunizing ferrets and mice. Ferrets after recovery from infection were resistant for at least 3 months, after which the immunity slowly waned. In this latter period there remained virus-neutralizing antibodies in their serum but the nasal mucosa was still susceptible to virus. Subcutaneously injected virus gave these animals once more a full resistance. They were able to produce a partial immunity in ferrets by subcutaneous injections of living or formolized virus so that antibodies appeared in the blood and after intranasal inoculation of virus the lungs were not affected. Ferrets developed lung lesions when swine influenza virus was given in the nose with, and often without, ether. Neither of the human viruses gave lung lesions in ferrets at first, but W. S. was modified by serial passage using ether until it also

did. In all these experiments the controls were untreated before the test and in the titration for neutralizing antibodies the controls were given virus in saline. Mice immunized by two fortnightly subcutaneous or intraperitoneal living virus injections and tested 8 days after the last, showed no symptoms, but 7 of 12 had lung lesions and in 5 of these the lesions were of the same extent as in 2 of 6 controls. The controls received no previous treatment and were all ill after the test virus inoculation. In a larger group after subcutaneous vaccinations and tested in 10 days only 2 of 24 showed a small lung lesion, after two similar vaccinations and tested 23 days later 5 of 20 gave slight to moderately severe lesions while of 24 controls with no previous treatment 9 gave similar lesions, 10 none and 5 severe fatal lesions. The evidence in this report for the differences between the swine and the human virus is based on incomplete neutralization by heterologous sera. Eleven human convalescent, 6 of 8 normal, and 5 of 6 human placental serums neutralized the W. S. virus and 2 human convalescent and 1 normal serum neutralized the swine virus while 1 human placental serum did not. They hope that a vaccine applicable to humans may be developed.

Francis and Magill (1935)[2] gave a warning that it is necessary to quarantine newly bought ferrets for 2 to 4 weeks, since some of them develop purulent rhinitis and may carry hemolytic streptococci or Gram-negative bacilli. These workers found one shipment of ferrets resistant to experimental virus infection, another lot susceptible and a third on arrival exhibited nasal discharge—all these animals coming from the same breeder. Some of this latter group were also resistant to active virus and the virus after inoculation could not be recovered from them, while with others a moderate fever and other symptoms lasting 3 to 4 days followed inoculation, but again the virus could not be transmitted by inoculation of lung or turbinate suspensions into susceptible ferrets. Two of these ferrets whose serum neutralized the virus were given the virus per nose with negative results, and the lungs and turbinates of one of these failed to give disease to a normal. They assumed that these ferrets had become immune in some unknown way and it is unfortunate that no ferret virus was obtained from any of them at the time they exhibited a nasal discharge. Of course it is just possible that this lot of ferrets was recovering from distemper. (See a later discussion.) These workers succeeded in producing serum-neutralizing antibodies in rabbits which species is not susceptible to infection. Mice were also immunized by subcutaneous, followed by intraperitoneal inoculation of living virus in lung tissue, and controls similarly inoculated with normal lungs developed no such immunity as shown by the fact that after intranasal inoculation of virus all the latter showed lung lesions, and none of the former. Neutralization tests with the serum of patients before and after recovery from influenza, pneumonia and the common cold suggested a specific response to infection with the virus of influenza only in the case of influenza. In 3 influenza patients the sera neutralized the virus for mice during convalescence and 6 months later, but not in the acute stage. In 8 pneumonia cases the power of the serum varied from complete to almost no neutralization, but in only 1 did this increase during convalescence. In 4 cold cases the serum before, during and after the affliction remained the same, and in 1 it gave complete neutralization in each test.

Laidlaw (1935) in his Linacre lecture on Epidemic Influenza gave a number of interesting facts. The virus was destroyed at 56° C. in 1 hour, and was resistant to drying and storage in 50% glycerol. It was only recoverable from the lungs and upper respiratory mucosa. In animals without ether it was not fatal. Certain streptococci increased its severity but H. influenzæ did not modify the disease. There was no evidence that in this last observation fully virulent cultures were used. He explained the lack of contagiousness in mice on the bases that the nose was unaffected and sneezing did not occur. (In the epidemiology of influenza, however, sneezing or coughing is not the sole explanation of the high contagiousness.) The failure to obtain virus from all cases of influenza he believed is due to an insufficient amount of virus in the nasopharyngeal washings, because the ferret is less sensitive than man, or on account of the varied resistance of the human population. His final view is that the virus may cause the mild short disease and that with the hemoglobinophilic bacilli the sinusitis, purulent bronchitis and pneumonia follows—if the bacterial factor were varied, he said, this would explain much. He suggested that a variant of the local virus may be the cause of epidemics.

Elkeles (1935) was successful in transmitting human influenza to suckling pigs, using intranasal inoculation of the virus before and after ferret passage. The pathologic picture produced in pigs was the same as that described for ferrets by the English workers, but the course of the disease was more severe when virus and influenza bacilli were used. The influenza bacilli alone had no effect. He advised the use of suckling pigs for these virus experiments as being more suitable than ferrets since they react more easily.

Francis and Magill (1935)[3] reported the cultivation of the P. R. 8 strain of human virus after 44 passages in white mice. Lung preparations in Tyrode's solution were centrifuged and filtered through a Berkefeld V candle and the bacteria-free filtrate seeded into chick embryo Tyrode's medium, and serial transfers made every 48 hours. Mice inoculated intranasally with the 10th and up to the 20th subculture developed pulmonary lesions. Cultures were also passed through mice and again cultured from these with similar results. A ferret also responded typically to an inoculation from the 7th culture. The cultured virus was inhibited by the sera of ferrets recovered from infections with the P. R. 8, the Philadelphia or the new Alkaska strain of virus and not by normal ferret serum. The uninoculated medium was entirely innocuous for mice. They noted certain alterations in the immunologic characteristics of the virus after repeated cultivation *in vitro* and this is to be investigated.

Noble and Brainard were able to produce symptoms of a mild respiratory disease in 4 of 12 ferrets by inoculation with filtered bacteria-free nasal washings from human cold cases and apparently to transmit this condition from a ferret to a human being. One attempt to transmit it serially from ferret to ferret was unsuccessful.

Summary of the Influenza Virus Studies. 1. The virus of swine influenza is contagious by pen contact in swine. It is not definitely so in ferrets or mice.

2 The pure virus disease in swine is relatively mild but the epi-

demiologically complete disease follows the mixture of virus and influenza bacilli.

3. The virus obtained from man also produces the characteristic disease in swine under the same conditions as the swine virus.

4. Human viruses, giving a disease in ferrets and from ferrets in mice, have been obtained from various parts of Great Britain and in America from Puerto Rico, Philadelphia, New York and Alaska. Immunologically all these strains act alike.

5. The pure virus disease in animals is mild and the epidemiological evidence that the responsible virus is the causative factor in human influenza is incomplete. No clear proof has been given that influenza bacilli or other bacteria are involved in the disease in animals but little has been done with fully virulent H. influenzæ in this phase of the problem.

6. The virus lung lesions without, but particularly after, the preceding use of ether are not accepted as specifically a virus lesion.

7. The virus disease in ferrets is not specific for virus infection but would seem a type of response in the ferret to a number of agents.

8. The virus has not been obtained from all cases of clinically diagnosed influenza and the arguments that the negative results are due to faulty diagnosis, to scarcity of the virus, or to varying resistance applies equally well to the influenza bacillus theory. There can be no doubt that a variety of influenza-like diseases has a variety of etiologic agents and the problem is primarily whether or not pandemic influenza has a constant etiology.

9. Viruses with very similar characters have been obtained from other diseases such as the common cold. These might be, of course, less virulent strains of a common virus. This is the only evidence that a possible reservoir for the virus in interepidemic times has been found, and is obviously rather weak. There is no method today available for discovering viruses in non-virulent form.

10. The investigators who have used the immunologic evidence as favoring the virus theory have not sufficiently analyzed: the anatomic and physiologic background in the intranasal neutralization experiments and in the passive immunity tests; or the reflex effects of extra-respiratory injections; or the possible sensitizations and the effects of protein or foreign serum shock; nor have most of the controls been satisfactory.

11. No adequate evidence to account for the toxicity of clinical influenza has been suggested.

Nevertheless, most valuable data are now available from these virus studies of influenza bearing on the resistance of recovered animals and the presence of neutralizing antibodies in relation to this and to recovery in man, so that the virus theory is certainly gaining ground and may serve at least to differentiate certain respiratory diseases from others. Very few other epidemics have been adequately explained even when the etiologic factors are known so that we must not demand too much at this early stage of the virus investigation of influenza.

Other Virus Diseases of the Respiratory Tract. *Distemper.* The use of ferrets for the isolation and identification of the virus of dog distemper by Dunkin and Laidlaw, the natural susceptibility of these

animals to distemper and their predominant use in the study of the human influenza virus make it advisable briefly to refer to certain reports bearing on a possible relationship between the two viruses. Distemper is usually a respiratory disease and has many clinical and epidemiologic resemblances to influenza. Bemelmans (1932) considered these two diseases as well as pleuropneumonia of horses as practically identical, largely, it is true, on theoretic and philosophic grounds. The virus, however, produces the disease in animals after subcutaneous and other routes of injection, and in infected animals the virus is found widely distributed in the blood and other tissues.

Nicolle (1931) inoculated subcutaneously a man, a monkey and a young dog with defibrinated blood of a dog ill after inoculation with distemper virus. The dog developed the typical febrile disease on the fourth day. On the sixth day blood taken from the man and the monkey (neither having shown any symptoms) was injected intraperitoneally into two dogs under isolation. The dog which received the blood from the man developed the disease and its blood was infective for two other dogs. The dog receiving the monkey's blood remained well. Nicolle concluded from this evidence that man can be infected with this virus but without showing any symptoms, and that under certain circumstances he can play the rôle of a virus carrier particularly dangerous, perhaps, because unrecognized. The philosophic conclusion he drew from these observations was that dog distemper had been a primitive disease of man effaced little by little from human pathology as a result of the hereditary immunity following repeated attacks, but that the disease is relatively new in the dog and attacks it with severity. It is unfortunate that nasopharyngeal washings were not tested for the virus in this experiment. On the basis of this report Remlinger (1933) suggested that sporadic distemper in dogs may be derived from human carriers and that the blood of man, probably containing antibodies, might be used to treat infected dogs. I have not found any evidence that such has been tried. Norr (1935), in a study of influenza-like diseases of animals, referred particularly to distemper which attacks dogs, cats, ferrets, monkeys and other animals. He said there had been a steady increase in Munich since 1934 of the nervous form of dog distemper—the most dangerous form of the disease—and considered the possibility that such an increased virulence might be related to outbreaks of human epidemic influenza. Both diseases are readily transferable to ferrets. He suggested that the serum of dogs recovered from distemper be tried in severe cases of human influenza and in any case that correlated facts be collected bearing on the periodic coincidences of these diseases in man and animals. Eichhorn and Pyle (1934) partly confirmed the results of Smith, Andrewes and Laidlaw, using a virus brought back from England which, on passage through ferrets, lost its infectivity for ferrets. All the ferrets recovering from the virus disease were not immune. A new supply of virus remained active and had been passed through a series of 30 ferrets. Two ferrets were inoculated at each passage and one was allowed to recover so that many recovered ferrets were available. Eleven of these latter were used for testing, by injection, a canine distemper virus and they were surprised to note that there was a delay in the onset of the disease from the usual

incubation period of 9 to 10 days to one of 13 to 17 days and 2 ferrets were apparently fully immune. A second series of 11 ferrets were given influenza virus by nose, and after recovery were injected with a known fatal dose of canine distemper virus. Four were completely immune, 4 others showed questionable immunity and death was delayed in all the others. Further studies by these authors on this suggestive problem are promised but I have not seen any later report. Schaaf (1935) also found that a previous infection of the ferret with the virus of human influenza increased the resistance of this animal to the virus of dog distemper in that the disease was less acute and death occurred very much later than in the controls. Smith, Andrewes and Laidlaw (1933) emphasized the importance of quarantining all ferrets for 14 days to prevent a latent distemper from giving rise to serious confusion and, in 1935, they had one of their experiments ruined by an outbreak of distemper in their ferrets. It would be interesting to know whether or not the spontaneously immune ferrets which Francis and Magill (1935)[2] encountered were recovering from distemper.

Other Viruses. It is scarcely necessary to do more than mention the lung lesions of other virus diseases. Psittacosis is well known with its lobular confluent pneumonia and clinical resemblance to influenza. The similarity of smallpox vaccine virus pneumonia in rabbits (Muckenfuss, McCordock and Harter) to epidemic influenza and interstitial bronchopneumonia in man has been described by McCordock and Muckenfuss. They produced two types—a hemorrhagic after concentrated, and an interstitial bronchopneumonia after dilute virus—and they discussed the resemblances of the former to the findings in acutely fatal cases of epidemic influenza and of the latter to the lesions accompanying influenza, measles and whooping cough in man, and in some cases of distemper in dogs. The latter type was only reproducible when bacteria were also injected with the virus, but they did not consider this lesion in any way specific for a particular virus or bacterium. Francis (1935)[1] referred to the confusion between certain cases of yellow fever and influenza. Francis and Magill (1935)[1] reported 3 cases of laboratory infection with the virus of Rift Valley fever in all of which a clinical diagnosis of influenza had been made. The disease was differentiated by: the demonstration of the virus recovered by intranasal inoculation of ferrets; the fact that it was found, and produced lesions, in other tissues than those of the respiratory tract, and further by the serum neutralization tests in mice.

General Discussion. The virus of influenza does not form inclusion bodies, nor does it produce as lasting an immunity as most other virus diseases. Until we know a great deal more about the nature of these disease producing agents our attitude towards the evidence should be extremely critical, and only the most carefully designed and controlled experiments should be accepted. It is a time for collecting facts not for drawing conclusions. A filterable virus as Hyde conceived it (1935) is an agent of particulate nature, of ultramicroscopic dimensions, it passes filters that retain vegetative forms of parasitic life, can be passed in series on sensitive hosts, produces characteristic inclusion bodies, cannot be cultured on lifeless media and would be unknown were it not for the changes produced in the body of animals and plants. The

limits of variation of viruses in different hosts and the modifications which result from differences in virulence are largely unknown, nor do we know if they exist in a quite avirulent and therefore undetectable form in carriers, nor whether these can be brought into activity by predisposing conditions.

The evidence for the three suggestive theories for the primary etiologic agents in influenza—bacteria, virus and virus plus bacteria—is here presented, and it is hoped that many of the unsolved phases of the problem will be more adequately dealt with in the event of another pandemic. The ideal method would be to have equally enthusiastic investigators of the different views study the same cases independently, since there are many hiatuses to be filled before the etiology of influenza can be established.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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IMPORTANCE OF IMMUNIZATION IN PREVENTIVE MEDICINE.*

The Common Communicable Diseases.—The field covered by the title above is one in which much has been accomplished and much is hoped for, but in which there have been many disappointments. It is a remarkable fact that smallpox vaccination, the first of the immunological procedures developed, should also have been the most successful, although it was applied long before immunology in its modern implications was known. It is also remarkable that immunizations against rabies, diphtheria, and tetanus were among the very earliest developments in the field of immunity and these, in a general way, are highly successful measures. The success attending these early applications of immunity in preventive medicine may account for the almost childlike faith with which many of the later developments have been welcomed, faith that often was converted into disillusionment on the basis of further observation. In considering the application of immunological procedures from the public health point of view, it is necessary to take into account factors other than the essential effectiveness of the proced-

* This material covers the substance of several addresses to medical groups. It has not been arranged with the customary references, which, however, can be supplied by the author on request.

ure. It would be foolish to attempt to immunize the entire population against whooping cough which practically is important only in the early years of life, or to immunize infants against typhoid fever since this is chiefly a disease of older age groups. This illustrates the importance of the age factor in planning an immunization campaign. Again, the disease may be one of so low an incidence in the community that it would be inadvisable to apply serum or vaccine prophylaxis generally. Obviously, it would be inexpedient to attempt general vaccination against rabies even if we had the means of doing this that were perfect—hence we vaccinate only those who have been definitely exposed. Finally, in this connection, we must remember that substantially all immunization procedures have certain risks associated with them, risks that must be carefully weighed lest we incur hazards in excess of those we seek to avoid. With these preliminary considerations in mind we may now turn to an appraisal of the status of certain procedures in the light of experience up to the present time. The various diseases will be considered somewhat in the order in which immunization procedures for them have been developed. No reference will be made to therapeutic application of immunological procedures.

Smallpox.—The question often is asked as to the duration of smallpox immunity. It has been a controversial point since the days of Jenner. A safe rule would require vaccination before a child had reached the age of 6 months, again before the age of 6 years, and thereafter only in the presence of an epidemic or when there is a threat of exposure. There are certain complications following smallpox vaccination that have attracted much attention during the last two or three decades. These complications were relatively unimportant as causes of disability and death but were taken as a ground or criticism on the part of anti-vaccinationists.

Postvaccinal Tetanus.—This, now very rare, was at one time sufficiently prevalent to be taken into consideration by all concerned with vaccination. The source of the infection, even after much investigation, still remains unknown. The disease was of marked severity, the death rate being 90% or even more. The incubation period, counting from the time of the insertion of the vaccine virus, was rather long, usually about 3 weeks. In a careful investigation by Dr. Armstrong of the United States Public Health Service, it was demonstrated that postvaccinal tetanus was found only when a dressing or shield was applied to the site of vaccination, although, of course, not all such applications were followed by tetanus. So, to prevent this complication, avoid dressings.

Postvaccinal Encephalitis.—The etiology of this is unknown. Perhaps the most plausible view regards it as virus infection remaining silent in the community and in the individual until something happens to activate it, the "something" being an infectious disease, in this case vaccinia. The symptoms usually come on from 7 to 14 days after the insertion of the vaccine virus, and essentially they are fever, headache, vomiting and other symptoms directly referable to the central nervous

system. The condition often is overlooked as it is easily mistaken for other acute nervous system infections, especially poliomyelitis or meningitis. This complication is extraordinarily rare in children under 2 years, hence the best safeguard is to vaccinate as early in life as possible. In some countries this complication has been so prevalent that local action has been taken permitting the restriction of vaccination.

Septic Infections.—Much less is known about these than about the preceding complications, but employees' compensation and other statistics attest their existence. Within recent years certain new methods for the propagation of vaccine virus have been introduced. While the calf vaccine which has given long and efficient service still remains the most popular agent, artificially cultivated vaccine virus which is propagated in the chick embryo tissue or the living chick embryo is being tried. It is too early to make a definite appraisal of the value of this type of vaccine virus.

Typhoid Fever.—Most of the information as to the efficiency of typhoid vaccine comes from military experience where the evidence indicates that it has proven extremely satisfactory. However, the experience in civil communities has been less satisfactory—so much so that a few years ago the American Public Health Association appointed a committee to study the whole subject of typhoid vaccination. When this report is completed and made public doubtless we shall have better information on the subject.

There have been modifications in the dosage of the typhoid bacillus and in the components of the vaccine as to the paratyphoids. It scarcely can be said that any one preparation is to be regarded as standard. That there has been dissatisfaction with the results of typhoid vaccination is shown by the studies being carried on by various research workers here and abroad in an effort to improve the vaccine. These studies are related to our growing knowledge of the complex nature of antigens and to the antigenic peculiarities of different strains of the same bacterial species. There, of course, has been a marked and gratifying reduction in our typhoid fever rates in recent decades, but it is very doubtful that immunization has been an important factor in bringing this about.

Diphtheria.—In connection with diphtheria prophylaxis it must be remarked that the disease takes its chief toll in children under the age of 6 and if prophylactic procedures are delayed until the child enters school the best opportunity for preventing infection has been lost. Passive immunity with diphtheria antitoxin once played an important rôle in the prevention of the disease. This practice is limited now to the few occasions in which it is impossible to keep those in contact with known virulent infection under close medical observation. In all diphtheria prophylaxis the importance of the Schick test must be borne in mind, especially after the immunization procedure has been completed. The mere injection of a person with one or more doses of a prophylactic is not a guarantee that immunity will be induced. It is appreciated, of course, that the Schick test is not an infallible index of diphtheria

immunity, but for practical purposes it may be considered as giving most useful information. The two preparations most in use at the present time are the Ramon toxoid, which is given in 2 or 3 doses at intervals of 3 or 4 weeks, and the more recently developed, refined alum precipitated toxoid which is given ordinarily in one dose. The latter, of course, has a great advantage in requiring but a single injection. On the other hand, it occasionally is followed by rather annoying indurations and even abscesses and thus far the research workers have failed to develop a means whereby this complication may be avoided.

Scarlet Fever.—Early work bearing on the streptococcus as the etiologic agent of scarlet fever was rather inconclusive but the work of Doctors Dick, Dochez and others has put the whole subject in a different light and on a sound foundation. Passive immunity induced by the injection of scarlet fever streptococcus antitoxin is believed to be inadvisable generally because of the low incidence of scarlet fever among contacts and the likelihood of serum reactions which appear to follow scarlet fever antitoxin somewhat more frequently than other antitoxins. Within very recent years serum from those convalescent from scarlet fever has been used for passive immunity; much success is claimed for the procedure but it is too early for final appraisal of the practice. Active immunity induced by means of several injections of a toxic filtrate developed from the hemolytic streptococcus of scarlet fever appears to be an effective measure for the prevention of the disease. This method of prophylaxis requires 5 injections in addition to a preliminary Dick test to determine susceptibility and another Dick test after the injections have been given to determine whether the immunization has been successfully accomplished. This means that the physician must see the patient seven times. Most health departments have found it impracticable to attack scarlet fever in this manner, but it would appear that this is peculiarly a field where the private physician might recommend immunization of susceptible children among his clientele.

Whooping Cough.—The evidence is most contradictory on the efficiency of whooping cough vaccine. The disease has its prevalence chiefly in those of tender years, the highest mortality being during the first 2 or 3 years of life. The older whooping cough vaccine preparations probably were of little or no value. Certain newer preparations that have come into use in recent years seem to offer more promise, but even these can hardly be said to have become well enough established to justify widespread general application. Stress is laid on certain details of manufacture, which perhaps cannot be practiced readily in large scale production.

Measles.—It seems to be quite clear that it is practicable to prevent measles by giving to exposed children serum from persons recently convalescent from the disease, or even serum or whole blood, of adults. The dosage and time of administration of the serum must be chosen carefully to secure the most favorable results. If the serum is given immediately after exposure, an attack of measles is likely to be avoided and the child will have only a temporary immunity. If it is given from

5 to 8 days after exposure, a mild attack of measles which is practically free from danger frequently ensues, resulting in a lasting immunity. Within recent months commercial preparations of human placental extract have been developed for use in measles prophylaxis; apparently the effect is much the same as that of convalescent serum.

Influenza, the common cold, meningitis, pneumonia, and poliomyelitis are all still beyond any practicable means of prevention, by induced immunization.

GEORGE W. McCOY, M.D.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA,

SESSION OF JANUARY 20, 1936.

The Effect of the Adrenotropic Hormone of the Anterior Pituitary Upon Hypophysectomized Depancreatized ("Houssay") Cats.—C. N. H. LONG and F. D. W. LUKENS (George S. Cox Medical Research Institute, University of Pennsylvania). The preparation of the purified adrenotropic hormone has been described by Collip, to whom we are indebted for our supply of the extract. Collip and others have shown that this extract is anatomically specific in causing a regeneration of the adrenal cortex following the atrophy which takes place after hypophysectomy in the rat. It is practically free of all other pituitary hormones as determined by anatomical methods. No metabolic studies have been reported with it to our knowledge. It does not restore hypophyseal cachexia even when adrenal regeneration is accomplished and produces no effect on the adrenal cortex of normal animals. The extract has been tested by us on 4 fed and 2 fasted Houssay cats in excellent condition. The fed cats were on a constant diet throughout the experiment. In both fed and fasted Houssay animals there was an increase of glucose and nitrogen excretion during extract administration, amounting to as much as three times the value of the excretion before and after the administration of the hormone. The nitrogen excreted was at all times more than enough to account for the glucose obtained. Ketonuria was absent throughout, since any ketogenic activity of the extract had been removed by boiling before use. The conclusion is reached that the adrenotropic hormone of the pituitary exerts a stimulating influence on protein metabolism. As far as glucose and nitrogen are concerned, these results are compatible with our previous reports of the effect of hypophysectomy and adrenalectomy on pancreatic diabetes.

The Effect of Adrenalectomy Upon the Response of the Rat to the Ketogenic Principle of the Anterior Pituitary.—EDITH G. FRY (George S. Cox Medical Research Institute, University of Pennsylvania). The increased ketonuria developed by normal, fasted rats in response to

injections of alkalin extracts of the anterior pituitary* was greatly reduced by adrenalectomy, whether the animals were maintained after operation on physiologic saline or on active extracts of the adrenal cortex. However, if the presence of accessory cortical tissue was either identified microscopically or indicated by long survival of the rat after withdrawal of saline or cortical extract therapy,* increased ketonuria resulted.

Long and Lukens have found that the spontaneous ketonuria of depancreatized cats was suppressed by hypophysectomy or adrenalectomy. Two explanations may be offered for these findings: *a*, The presence of the adrenal cortex mediates this ketogenic activity of the anterior pituitary; *b*, adrenalectomy suppresses the usual ketonuria by inducing structural and functional alterations in the anterior pituitary.

Saline therapy for adrenalectomized rats may not have prevented such alterations in the anterior pituitary, but cortical extract treatment which permitted normal growth should have prevented any such changes. Since the increased ketonuria was suppressed in both series, these results favor the first view that the adrenal cortex is directly concerned with the ketogenic activity of the anterior pituitary extracts employed.

Preliminary experiments indicate that rats respond to the same anterior pituitary extracts as well following thyroidectomy as before operation.

A Study of Gastric Emptying with an Open Tube in the Pylorus; Results with Liquids Including Olive Oil and N/20 HCl.—J. E. THOMAS and J. O. CRIDER (Laboratory of Physiology, Jefferson Medical College). Observations have been made on two dogs, provided with cannulated gastric and duodenal fistulas, under the following conditions: 1, Without apparatus (normal controls); 2, with an apparatus in the pylorus which maintains a 7-mm. opening, and 3, with an apparatus identical to the other externally but which does not open the pylorus (dummy controls). The apparatus consists of an aluminum tube held in the pylorus by means of narrow flanges and by rubber tubes passed through the gastric and duodenal fistulas. The cannulas are stoppered around the tubes so that leakage does not occur. Lateral openings in the tubing near the pylorus on each side complete the free communication between the stomach and duodenum.

The rates of emptying of normal saline, N/20 HCl and of olive oil were studied under each of the above conditions. There was no significant difference in the emptying times with the pylorus open as compared with the controls (normal and dummy) except that the emptying time of oil appeared to be prolonged somewhat when the pylorus was kept open. The following table gives the average emptying times so far recorded:

	Saline.		HCl.		Oil.	
	Dog 1. *Min.*	*Dog* 2. *Min.*	*Dog* 1. *Min.*	*Dog* 2. *Min.*	*Dog* 1. *Hrs.*	*Dog* 2. *Hrs.*
Normal controls . . .	18.5	21.25	41.6	48.3	4.66	3.0
Dummy controls . . .	17.5	22.5	44.4	45.0	4.2	3.0
Pylorus open	22.0	20.0	47.8	45.0	5.0+	4.0+

* We are indebted to the E. R. Squibb Company and the Upjohn Company for generous supplies of anterior pituitary and adrenal cortical extracts.

Experimental Pulmonary Edema.—VIRGIL H. MOON and DAVID R. MORGAN (Laboratory of Pathology, Jefferson Medical College). Pulmonary edema is found regularly at postmortem in man when the shock syndrome has preceded death. It is seen frequently in experimental shock when death was somewhat delayed. These facts suggested means for producing pulmonary edema experimentally. Shock with delayed death was produced by implanting muscle substance in the peritoneal cavity, by sublethal burns, by the injection of bile and of bile salts intravenously or intraperitoneally, by intestinal obstruction, barbital poisoning, and by repeated subcutaneous injections of histamin in dogs. In each instance hemo-concentration of 30% to 40% developed and the postmortem findings were those regularly present following death from shock.

Marked pulmonary edema was present in each animal so treated. The edema fluid had high specific gravity closely approximating that of the blood serum. Beginning pneumonia was seen frequently in the dogs which survived treatment longer than 4 days. The lungs were closely similar to those seen in man following burns, severe infections, intoxications, and so forth. Such edema results from increased vascular permeability and its mechanism of development apparently is integral with that of shock.

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

APRIL, 1936

ORIGINAL ARTICLES.

THE EFFECT OF LIVER EXTRACT ON THE SMALL INTESTINE OF PATIENTS WITH SPRUE.

By D. K. Miller, M.D.,

AND

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(From the Hospital of the Rockefeller Institute for Medical Research.)

A clinical study of a relatively large group of patients with sprue has been made over periods of from 1 to 3 years following remissions of the disease induced by liver extract therapy. During this study it has been observed that flatulence, intestinal discomfort, cramps and diarrhea recurred unless a sufficiently large amount of liver extract was administered at frequent intervals. This was the case despite the fact that no detectable hematological disturbance was present. Thus the intestinal dysfunction rather than the anemia has been the guide for the administration of therapy. The fact that the amount of liver extract necessary to prevent recurrence of intestinal dysfunction was far greater than that necessary to maintain normal blood levels, suggested that a relationship existed between liver extract and intestinal activity. The results of the roentgenologic study of an individual case which are presented in this communication bear out this suggestion.

Characteristic morphologic alterations of the small intestine of patients with sprue have been demonstrated roentgenologically by Mackie, Miller and Rhoads.[1] The extent of the abnormalities were shown to vary directly with the severity of the clinical picture and furthermore a return to a state more nearly normal was demonstrable after adequate therapy had been administered. These

abnormalities may be summarized as follows: 1, a segmental distribution of barium, produced, it is inferred, by abnormal motility of portions of the small intestine; 2, a variation in contour and caliber of the intestinal segments; 3, a distorted mucosal pattern, especially of the duodenum and jejunum, but often of the ileum as well; 4, an outline of the terminal ileum which appears straighter than normal and gives the impression of a lack of pliability of the intestinal wall.

In the course of this study an opportunity was presented for the investigation of a patient who had diarrhea regularly if liver extract was withheld for periods of from 10 days to 2 weeks. In this instance the changes in the small intestine were visualized by Roentgen ray both during an attack of diarrhea and immediately following the cessation of symptoms which followed liver extract therapy. The results are striking in that they furnish unequivocal evidence of the specificity of liver extract therapy of the intestinal manifestations of sprue without anemia.

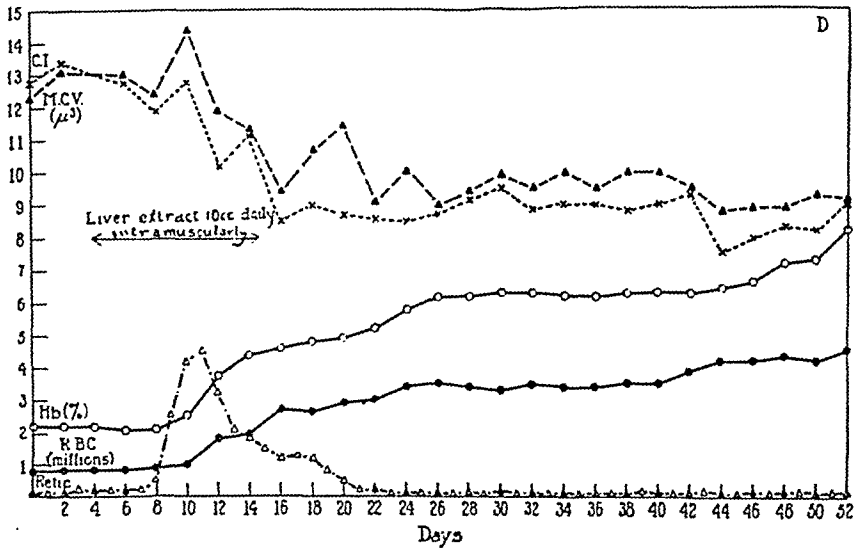


CHART I.—Hematological changes following the daily administration of 10 cc. liver extract intramuscularly.

Clinical History (Chart I). An American woman, aged 50, who had lived for 21 years in southern China, entered the hospital complaining of diarrhea of 7 years' duration. Her illness began with an acute, afebrile attack of diarrhea lasting 6 weeks. Subsequent attacks occurred during the first year. Early in the second year, soreness of the mouth and the tongue developed, and the diarrhea was persistent. Relief of symptoms followed the use of a diet of sour milk and liver. During the fourth year of the illness improvement did not follow the same treatment and the patient returned to this country, where she was symptom-free for 6 months. This period of relief was again followed by severe abdominal distress and diarrhea. About 6 weeks before entry, weakness, shortness of breath and pallor appeared, and she was confined to bed. Three vials of liver extract, Lilly, were administered orally each day without improvement.



FIG. 1.—Roentgen ray of small intestine 2¼ hours after barium meal during an attack of diarrhea showing two columns of barium and residue in stomach.

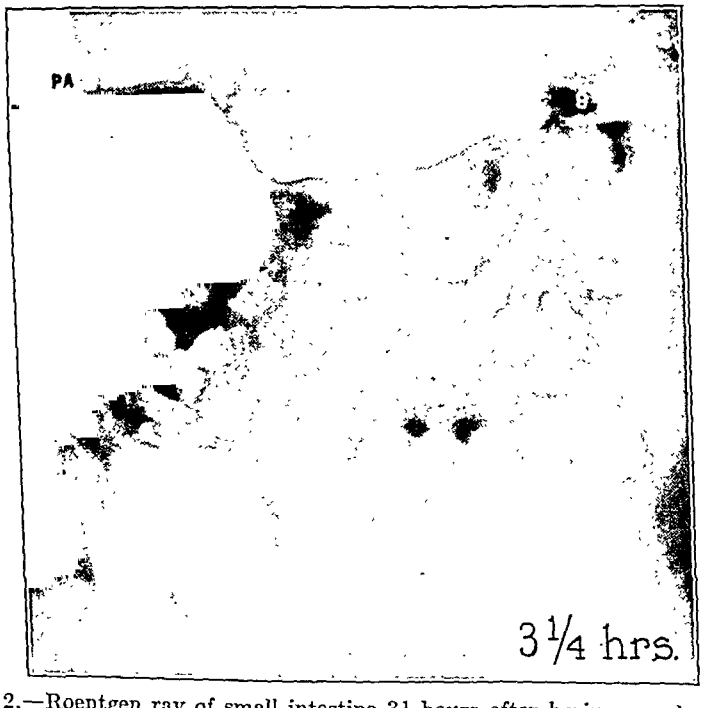


FIG. 2.—Roentgen ray of small intestine 3¼ hours after barium meal, during an attack of diarrhea, and showing segmental arrangement of barium in the ileum.

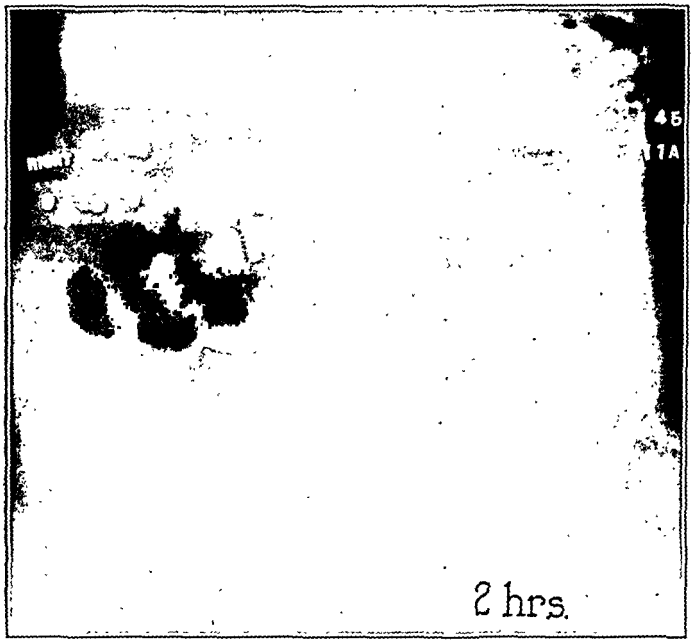


FIG. 3.—Roentgen ray of small intestine 2 hours after barium meal, 4 days after preceding Roentgen ray study and after diarrhea had ceased (compare with Fig. 1).

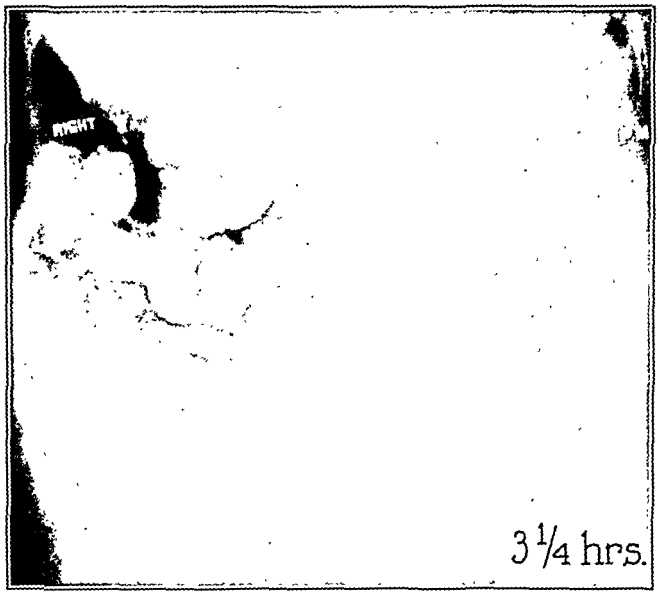


FIG. 4.—Roentgen ray of small intestine 3¼ hours after barium meal and after diarrhea had ceased (compare with Fig. 2).

Examination. The patient was markedly emaciated and appeared extremely ill. The skin and mucous membranes had a lemon-yellow tint and were pale. There was atrophy of the papillæ along the borders of the tongue, with furrows over the dorsum. The abdomen was slightly distended and tympanitic. The spleen was palpable. There was pitting edema of both ankles. Gastric analysis showed free hydrochloric acid only after the injection of histamin. Laboratory examination showed: red blood cells, 820,000; hemoglobin, 22%; color index, 1.34; mean corpuscular volume, 131 cubic microns; icteric index, 20; reticulocytes, 1%.

Course in Hospital. Daily intramuscular injections of liver extract (Eli Lilly & Co.) were given for 2 weeks. Each injection was of 10 cc., an amount derived from 50 gm. of whole liver. On the 6th day after the first injection there was a rise in the number of reticulocytes to 42%. The day after the first injection the patient had one formed bowel movement, although there previously had been 5 or 6 loose stools daily. The rise in the number of reticulocytes was followed by an increase in the number of erythrocytes and the hemoglobin. The patient had no further diarrhea unless a longer period than 2 weeks elapsed between injections of liver extract. She was discharged 7 weeks after entry with an erythrocyte count of 4,170,000 and a hemoglobin of 73%.

The patient has been followed for the past 3 years. During this time the erythrocyte count and the hemoglobin have been maintained at normal levels. There have been no diarrhea or intestinal symptoms except when a period longer than 10 days to 3 weeks elapsed between the injections of liver extract. The patient can determine the necessity for treatment by the appearance of flatulence, cramps and finally diarrhea. At no time has liver extract failed to relieve all intestinal symptoms within 24 hours.

The patient was readmitted to the hospital during an attack of diarrhea induced by withholding liver extract therapy. During this admission roentgenologic study of the small intestine was made and was compared to one done 4 days later, subsequent to the injection of liver extract and the relief of intestinal symptoms.

The method of Roentgen ray examination of the small intestine used in this study was that described by Mackie, Miller and Rhoads.[1] Two ounces of barium were given to the patient 1 hour after a light breakfast. Roentgen ray pictures were taken 15 minutes later and at 30-minute intervals the head of the barium column had reached the cecum. Reëxaminations were then made at hourly intervals until the small intestine was empty. The barium was given after a meal so that the motility of the small intestine would be as normal as possible.

The Small Intestine During an Attack of Diarrhea (Figs. 1 and 2). At ¼ hour the second portion of the duodenum was dilated and the rugæ were wider than normal. At 1¼ hours the upper jejunum showed a definitely abnormal mucosal pattern and was widened. A segmental progression of the barium was indicated by two distinct segments of small intestine which contained the radio-opaque substance. At 2¼ hours an even more marked segmental distribution was in evidence, as well as a variation in caliber and an irregularity of the contours of the isolated intestinal segments. At 2¾ hours the upper jejunum was empty and a segmental distribution of barium throughout the whole small intestine distal to the upper jejunum was found. Marked variation in caliber of these isolated segments was apparent, some being constricted and others markedly dilated. These changes are frequently seen in sprue and are almost invariably found when diarrhea is present. The barium reached the cecum in 5 hours, while at 6¾ hours a definite gastric residue was seen in the stomach, and the terminal ileal segments still contained barium.

The Small Intestine Subsequent to the Administration of Liver Extract Followed by Cessation of Diarrhea (Figs. 3 and 4). At ¼ hour and 1 hour

the same changes in the duodenum and jejunum were seen as in the previous study. At 1 hour, however, the stomach was nearly empty and the barium appeared to be travelling through the small intestine in a continuous column. Marked variations in the caliber and outline of the intestine were present. At 2 hours the stomach was empty. The head of the barium column had reached the cecum at $2\frac{3}{4}$ hours. No segmental distribution of barium was seen. At 5 hours the small intestine was empty.

The segmental distribution of the barium throughout the small intestine which was such a striking feature in the previous study had disappeared. The barium presented a continuous smooth outline throughout the small intestine. These changes are interpreted as indicating a restoration toward normal of the motor function of the small intestine.

Discussion. The study presented demonstrates an effect of liver extract on the functional activity of the small intestine in patients with sprue. The arrangement of the radio-opaque substance in isolated intestinal segments which was seen when diarrhea was present was not a feature 4 days later, after liver extract had been administered and diarrhea had ceased. Similar results have been seen in other patients of this series, but in none was the picture as dramatic as in this instance. These results demonstrate the therapeutic specificity of liver extract in sprue without anemia.

Clinical observation has shown that patients with sprue[2] or pellagra[3] require much larger amounts of liver extract than do patients with pernicious anemia. This applies even to liver extract therapy administered parenterally, a route which excludes the possibility of a lack of absorption or of destruction of the material in the gastro-intestinal tract. This fact, together with the observation that in patients with sprue a much larger amount of liver extract is necessary to prevent diarrhea than is required to maintain normal blood levels, suggests that either different fractions of liver extract are operative in sprue and pellagra from those which are effective in pernicious anemia, or that the therapeutic actions of the same substance varies in the three disease states. The conditioning of the functional activity of the small intestine may possibly be another therapeutic function of the antipernicious anemia substance. The answer to this problem awaits further investigation.

Summary. 1. Roentgenologic evidence of abnormal form and function of the small intestine of a patient with sprue, without anemia but with diarrhea is presented.

2. A return toward normal form and function, as evidenced by roentgenologic study, as well as the disappearance of symptoms followed the injection of liver extract.

3. It is suggested that liver extract administered parenterally conditions the functional activity of the small intestine.

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ACUTE BASOPHILIC LEUKEMIA.

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It seems to be true that rare cell-type leukemias and leukemic states do occasionally occur. Subscribing as we do to the principle that in any given leukemia there is an abnormal, immature, imperfect leukoblastic type cell proliferating and invading without normal maturation,[11,12] in time and full experience, one would expect to find leukemia cells resembling every normal type. Resemblance only, partial, imperfect differentiation only, varying degrees of resemblance to be sure, not always even a recognizable resemblance, for leukemia cells are sometimes exceedingly primitive and bizarre.

Hay and Evans[1] review the few reported cases of eosinophilic leukemia adding an acute case of their own, all previous authenticated cases having been chronic ones. There has been added recently the case of McCowen and Parker,[2] an acute eosinophilic leukemic state with leukemic infiltrations showing eosinophils.

Joachim,[3] in 1906, reported 2 cases of chronic leukemia in both of which the percentage of "mast cells" was above 50%. The first was followed for 5 weeks, discharged, and lost track of; the second for but a 17-day period, but giving a history of a diagnosis of leukemia made elsewhere 7 months previously at which first examination some 500,000 leukocytes were found. The blood picture was that of an ordinary chronic myeloid leukemia except for the large number of "mast cells," as high as 83%.

Joachim's opinion was that the general symptoms being similar to other chronic myeloid leukemias except for the degree of basophilic increase, one should be loath to call it a separate type of leukemia. He reported it as an atypical leukemia, concluding that chronic basophilic leukemia is a variety of the common myelocytic variety. He found the prognosis more unfavorable, and the mast cells radioresistant.

General infiltration characteristic of the chronic leukemias was found at autopsy. It was noteworthy that he had great difficulty in staining autopsy tissues. The basophil or mast cell granules disappeared. He got his best results with polychrome blue, but even then the granules were not distinctive. Such granules as were preserved showed varied stain affinity, from clear violet to bright red, like eosinophilic granules.

Sabrazès[4] was most interested in proving the differentiation of hemohistioblasts to mature mast cells. The so-called hemohistioblast of Ferrata and many types of basophils he had frequently found increased in chronic myeloid leukemia. He concluded that his case was one of chronic myeloid leukemia with an abundance of "granular basocytes." He believed such cases are relatively common and particularly resistant to both Roentgen ray and benzol. Using May-Giemsa stain, he noted variations in size of cell, size and distribution of granules, and a varying character of nucleus convincing him that he had supporting evidence in agreement with his previous views.[6] He maintained that mesenchymal hemohistioblastic cells have the capability of differentiating directly into the common granular basophilic cells. The blood in his case returned almost to normal after Roentgen ray treatment, except for the persistence of mast cells and the so-called hemohistioblasts. Four months after the first examination,[5] mouth lesions, cough, fever and a leukemic blood picture appeared. There were even more mast cells and hemohistioblasts than before, definite left shift in the leukocytes generally, and a severe anemia. No marrow biopsy is reported. The platelets were uneven and few in number and many of these few were large and globular. Among the white cells mitotic figures were said to have been found, the type of cell unfortunately not stated. Eventually the myeloblast became the dominant cell, 32% of the total number, the mast cells 20%.

Sabrazès[6] discussed the morphologic characteristics of basophilia under pathologic conditions. His observations and those of Di Guglielmo[7] may lead us away from our present not too clear conceptions of the origin of basophils, mast cells and, incidentally, monocytes.

Sarzi-Sartori's[8] case is practically a counterpart of Sabrazès'. He agrees with Joachim that one should be cautious about calling these cases mast-cell leukemia. His case showed 45% basophils and many hemohistioblasts. Although he had never seen the cell described by Di Guglielmo[5] on which Sabrazès sets great store, he accepts their theories.

Elliott and Young[9] reported a case called chronic mast-cell leukemia because of predominance of leukocytes with coarse basophilic granulation. They speak of the frequency of association of increase of both eosinophils and basophils in chronic myeloid leukemia and would restrict the term "mast-cell leukemia" to those

cases in which the basophilic leukocytes are the principal feature of the blood smear. The basophils reached 64% and were very coarsely granulated and mature. Roentgen ray treatment and benzol decreased the total leukocytes principally by reducing the adult neutrophils. The basophils steadily increased. Autopsy was referred to as revealing a splenic infarction but no other details were given.

Our case may be summarized as follows:

Case Report. A man, aged 27, dentist, was referred by Dr. Frank Stradling, Earlville, N. Y., September 13, 1935. He stated that March, 1935, he tired easily and lost weight. Appetite was poor and he slept fitfully. There was gastric distress, belching, and abdominal distention and a hard mass in the left upper abdominal quadrant. He noticed spongy gums with some bleeding and there was nosebleed. Having had laboratory training, he thought of the possibility of leukemia, examined his own blood and made his own diagnosis. He was seen by Dr. Roy G. Pfotzer, of Buffalo, N. Y., March 29, 1935, who noted: "He complained of malaise, anorexia, loss of weight, loss of color and a lump in the left side. Pale, well developed, fairly well nourished, the spleen was at the level of the umbilicus; temperature, 100.2° F. A blood count showed: Hb. (Dare), 64%; R.B.C., 3,800,000; W.B.C., 186,000; polys, 60%; myelocytes (principally neutrophilic), 35%; lymphocytes, 5%. A rare blast form was noted. At this time no basophilic element was present.

	W.B.C.	Myelocytes, per cent.
April 2	85,000	18
10	80,000	17
22	12,600	4
May 6	6,400	1
20	6,800	1
June 1	5,600	1
17	9,400	5
30	14,200	6

"His weight at first examination was 185; on June 30, when last seen, it had risen to 210, and at this time his R.B.C. was 4,540,000; Hb., 94%. The spleen receded and was not palpable on April 22. At no time during the blood studies was there a basophilic tendency."

He had 9 light Roentgen ray treatments to the splenic area (Dr. J. M. Barnes, of Buffalo), and large doses of iron by mouth. He was told that his blood was practically normal, but warned of recurrence and instructed to continue under observation. July 19, 1935, at the Norwich, N. Y., Hospital, his blood showed: W.B.C., 10,200; small lymphocytes, 16%; large mononuclears, 3%; neutrophils, 78%; eosinophils. 1%; basophils, 2%. Again there, August 21: W.B.C., 9500; lymphocytes, 20%; mononuclears, 4%; neutrophils, 74%; basophils, 2%.

About September 1 he began having gastro-intestinal disturbances, restlessness and all the other symptoms previously described, including the firm abdominal mass. Dr. Johns, Utica Memorial Hospital, reports, September 7: W.B.C., 39,500; polys, 67%; filament cells, 8%; non-filament cells, 59%; lymphocytes, 18%; transitionals, 3%; basophils, 12%; abnormal erythrocytes, none; abnormal leukocytes, myelocytes, also myeloblasts, 50 cells in 100.

On the strength of this blood finding he had a Roentgen ray treatment of 185 R's broadly over the left abdomen, given by Dr. Lee Hadley.

Dr. Stradling felt that the symptoms had suggested a possible peptic ulcer or malignancy in addition to the leukemia.

Physical Examination (Dr. Groat).—A remarkably well-built, clear-skinned, alert young man, 6 feet 3 inches tall, still weighing just over 200 pounds. Restless and apprehensive, but truly remarkably well in hand considering the fact that he knew all about his condition. The gums were soft, spongy and there were small clots in the margins next to the teeth; there were some small areas of ecchymosis on the buccal mucous membrane and a small clot behind the anterior pillar of the right tonsil. There was a multiform erythematous rash with itching, quite like an allergic rash, possibly due to the considerable amount of phenobarbital taken the previous 2 weeks. The neck, chest, lungs, mediastinum and heart appeared normal. A mass, evidently an enlarged spleen, reached 12 cm. below the left costal border and well toward the midline. There were some good-sized ecchymotic areas on the back; there was definite epigastric tenderness with tympanites and distention. The liver lower margin could just be felt. There were no palpably enlarged lymph nodes. The urine and blood aside from the abnormalities shown in the tables were not remarkable.

Progress. Continuous fever, increasingly bothersome nasal hemorrhages and oozing, bloody vomitus and new areas of ecchymosis. Frequent epigastric distress relieved somewhat by CO^2 and oxygen and he expired in coma at 5 P.M., October 5. Temperature ranged from 99.6° to 101° F. the first week, reached 103.6° F. following a transfusion in the second week, more irregularly, 100° to 103° F., during the third week and continuously 101° to 102° F. the final week, the pulse gradually working upward from the 80's to a running pulse of 120 to 140 in the final week.

Treatment. Since both general condition and blood state became definitely worse following the Roentgen ray treatment, acute leukemias being seldom benefited thereby, no further treatments were given. Twice a citrate transfusion of 300 cc. of blood was given and after each the patient was decidedly uncomfortable, once alarmingly depressed and at no time appreciably benefited despite the fact that the blood was carefully matched. The reactions were 24 to 48 hours afterward in both instances, the temperature rising to 104° F. without chill. He desired not to have any more transfusions and it seemed humane not to insist upon them in any revised form.

The only medication, other than sedatives, was liver extract intramuscularly, which in our experience has been somewhat helpful in other cases of acute and chronic leukemia, more particularly in the latter. But these injections were discontinued during the last week because they became so objectionable to the patient. He asked to have iron, so a preparation of citrate of iron was given him by mouth the last few days. This placebo of iron seems to account for the black, granular, semisolid stools which he had on the last day.

Necropsy (Dr. Wyatt, 2½ hours after death). On external examination the only significant findings were marked pallor of skin and mucous membrane and a small healing puncture wound over the middle of the head of the sternum made for marrow biopsy. The serous cavities showed no significant lesion. There was rather marked pallor of the myocardium, liver and kidneys, without other gross lesion. The lungs showed numerous small scattered hemorrhages but no gross evidence of inflammatory or leukemic infiltration. The spleen was rather markedly enlarged, weighing 1045 gm. On section its cut surface was fairly firm but somewhat friable, and the normal splenic markings were not evident. In the duodenum just beyond the pyloric ring there were two separate, typically punched-out, peptic ulcers, each of which measured approximately 1 cm. in diameter. One of the ulcers was on the superior wall and was firmly

adherent to the neck of the gall bladder, while the other was on the posterior wall and was adherent to the pancreas. There were no large bloodvessels exposed in the ulcers. The contents of the intestines were somewhat blackish, but not definitely tarry in consistency. (Iron citrate had been administered.)

The bone marrow as observed in the ribs and head of the sternum was not remarkable in its gross appearance. The marrow cavity of the middle third of the right femur was filled with abundant, rather firm, mottled reddish and grayish marrow which was definitely adherent to the walls of the cavity. The inner surface of the compact bone forming the wall of the marrow cavity was distinctly roughened, due to the presence of a layer of marrow, 1 to 2 mm. thick, which was mixed with loose, spongy bone. Direct smears of the marrow from the femur, ribs and sternum were made, in addition to the taking of blocks of tissue for sections, which were prepared with the usual paraffin technique and stained with hematoxylin and eosin.

Microscopic Findings. There was slight degeneration of the myocardium, but not to the degree which was suspected from the gross pallor and mottling. The sections of the lungs showed hemorrhage, slight edema, and small areas of bronchopneumonia. There was no evidence of leukemic infiltration in the sections of myocardium, lungs, or kidneys. The walls and floors of the duodenal ulcers showed only inflammatory reaction and necrosis, without definite invasion by leukemic cells.

Spleen. There was complete loss of normal splenic architecture and replacement by a picture very similar to that seen in the bone marrow. This was made up of more or less evenly distributed leukoblasts of various types, erythroblasts, a few megakaryocytes, intermingled with mature leukocytes and stroma cells. In places there was more or less fibrosis. The cells which stood out most clearly and were most easily classified as myelocytes were eosinophilic. These were quite numerous. In addition, there were numerous other cells of about the same size and with nuclei of about the same character, but without definite granules in the cytoplasm; these were presumably either neutrophilic myelocytes or basophilic myelocytes which had undergone such changes in the cytoplasmic granules as to render them undemonstrable in those sections. The presence of such basophilic cells in large numbers in the direct smears of marrow and their absence in the sections of marrow and spleen, even when stained with the same blood stain as the smears, would suggest that the granules are easily lost in the preparation of sections. This has also been the experience of others in studying similar cases.[3] In addition to these myelocytic cells there were numerous larger cells with a small amount of non-granular cytoplasm which probably were myeloblasts. In certain instances these seemed to be definitely grouped to form areas which stood out from the surrounding cells. Erythroblasts were relatively inconspicuous, as were also the megakaryocytes.

Liver. In the connective tissue of the portal canals there was considerable myeloid tissue similar to that described in the spleen. There was also definite necrosis of liver cells in varying degrees in the centers of the lobules.

Bone Marrow. The marrow was very cellular, the leukoblastic elements markedly predominating over the erythroblastic, giving the impression that the latter were crowded out. The structure was somewhat similar to that described in the spleen, except that it was more cellular. Eosinophilic myelocytes were present in large numbers; also there were very numerous myelocytes which were probably divided between the basophilic variety shown in the direct smears and the neutrophilic type. There were also very numerous large atypical cells, probably of primitive myeloid type. Megakaryocytes were found rather infrequently, and for the most part

tended to be young, active forms. The grouping of myeloblasts or myelocytes of a certain type was rather striking in places, large fields being made up almost entirely of similar cells. Mitotic figures were found rather frequently in certain areas of the sections whereas in other portions they were found infrequently. It was difficult in all instances to be sure of the type of cell in mitotic division; but some of them were large and nongranular while others were smaller and probably myelocytes of either the neutrophilic or basophilic type and very few erythroblasts. No mitotic figures were found in eosinophilic myelocytes.

Summary of Macroscopic and Microscopic Findings. Some degeneration of myocardium. Bronchopneumonia. Two duodenal ulcers. Splenomegaly with myeloid leukemic infiltration. Some leukemic infiltration in portal canals of liver. Central necrosis of liver. Myeloid hyperplasia of bone marrow, largely replacing erythroblastic tissue and megakaryocytes.

TABLE 1.—(MISS F.)

Date, 1935.	Hemoglobin.	R.B.C.	W.B.C.	Neutrophils.	Lymphocytes	Mononuclears.	Promyelocytes. Myelocytes. Metamyelocytes Neutrophilic.	Eosinophilic.	Granulocytes.	Basophilic.	Granulocytes.	Eosinophilic-Basophilic.	Granulocytes.	Myeloblasts.	Others.
Sept. 13	14.0	3.3	40.1	62.0	2.5	2.0	5.0	..		24.0		0.5		3.5	0.5
14	..	..	..	57.5	5.0	3.0	10.5	1.0		21.0		..		2.0	
15	..	..	..	54.0	3.5	3.0	11.5	0.5		26.5		0.5		..	0.5
16	..	..	..	50.5	2.5	3.0	10.5	1.0		32.0		..		0.5	
17	14.0	3.6	30.0	49.0	1.5	2.5	10.0	..		32.5		0.5		3.0	0.1
18	..	..	..	44.5	3.5	3.0	12.0	..		32.5		0.5		4.0	
19	..	..	..	42.5	1.0	2.5	16.5	0.5		32.5					
20	..	..	..	38.5	2.0	..	13.0	1.0		37.0		1.0		6.0	1.5
21	..	..	..	37.5	2.0	1.0	14.5	1.0		36.5		1.5		4.0	2.0
23	12.0	3.0	75.2	31.5	1.5	2.5	11.0	1.0		44.0		1.0		4.5	0.5
24	..	..	..	26.0	1.0	3.0	8.5	0.5		55.0		..		5.0	1.0
25	..	2.2	53.6	22.5	2.0	1.5	15.0	..		50.0		..		7.5	1.5
26	5.5	2.0	61.6	25.5	1.0	0.5	5.5	1.0		61.0		..		5.5	
27	..	..	..	23.5	2.5	0.5	10.0	2.0		47.5		1.0		11.0	2.0
28	5.5	1.7	86.7	24.0	..	1.5	11.0	2.0		48.0		..		11.0	2.5
29	..	..	..	15.5	0.5	1.5	11.5	1.0		58.5		0.5		11.0	
30	3.5	1.4	118.4	14.0	..	..	9.0	3.0		57.5		..		15.0	0.5
Oct. 1	..	1.3	96.0	19.5	..	..	5.0	1.5		58.0		0.5		13.0	2.5
2	..	..	..	17.5	0.5	..	10.0	3.5		51.0		..		13.0	4.5
3	..	1.2	121.6	14.0	..	..	8.0	1.0		54.0		..		19.5	3.4
4	..	..	..	13.0	..	..	6.5	4.0		58.0		..		17.0	1.5
5	..	950.0	..	19.0	..	..	7.0	3.5		41.0		1.0		25.0	3.0

The major progressive blood changes are shown in Table 1. The additional features are that the platelets were from the first sparse, apparently never over 80,000, and highly abnormal, mostly large globular, or dumbbell shaped with occasional long streamers, and very pale staining. They did not clump normally, possibly additional evidence of qualitative deficiencies.

Reviewing the progressive blood picture, it is noteworthy that the total number of cells and the total number of basophilic and myeloblastic cells increase roughly in much the same ratio (Table 2), with the anemia in reverse ratio. There is a non-progressive left shift in the neutrophils and a progressive left shift in the basophils (Table 2). An arbitrary division of the basophils was made to permit a differential count and indicate a possible shift. These type cells may be readily recognized in the photomicrographs in

Plate I. It is noteworthy that both the large cell with fine basophilic granules and the large cell with coarse basophilic granules show some variation in the size of the granules. This variation in granule size is more marked in the two smaller mature types. We do not include as basophils basophilic proeosinophils or basophilic proneutrophils, notwithstanding the fact that others have had difficulty in separating them. There were very few such cells in the smears and they were included in their own classes. This was possible because the stain which we use, a modification of Jenners' stain not dissimilar from the May-Giemsa in its actual composition and potentialities, we believe to be superior to all others as a differentiator of granules. The granules of basophilic proeosinophils with our stain are more pinkish violet and definitely less intensively stained than are true basophil granules which stain a purple black. This stain and its results have been demonstrated[10,13] and many now use it. An article describing its manufacture and use is soon to appear in the *Journal of Laboratory and Clinical Medicine*.[14]

TABLE 2.—(MISS F.)

Date, 1935.	Basophils, percentages.					Neutrophils, percentage.		Myeloblasts, total.
	Total.	Class I.	Class II.	Class III.	Class IV.	Total.	Non-filamented polys.	
Sept. 13	9,624	26	51	4	19	24,862	30.0	1,403
17	9,750	35	46	2	16	14,700	33.0	900
23	33,088	48	40	2	10	23,688	25.0	3,384
26	37,576	57	36	2	5	15,708	29.0	3,388
28	41,616	58	32	4	6	20,808	40.0	9,537
30	68,080	61	28	5	6	16,576	36.0	17,760
Oct. 1	55,680	60	35	2	3	18,720	23.0	12,480
3	65,664	67	26	4	3	17,024	29.0	23,712

Classes of basophils:

I. Large cells with fine granules over an immature nucleus.
II. Large cells with variating coarse granules over an immature nucleus.
III. Cells, slightly smaller, with variating coarse granules in the small portion of cytoplasm.
IV. Smaller cells with fairly typical granules over a more mature clover-leaf-shaped nucleus.

A sternal marrow biopsy was done, October 1, 1935. The method of choice, trephining a plug from the sternum for smear and section, was not followed because of certain objections, and also the possibility of hemorrhage; but the method used was comparable to it in that a 12-gauge needle with blunted point and trocar was thrust into the sternum, the trocar removed, the needle then advanced and rotated, then carefully withdrawn, removing a mush

of marrow from which the smears were made and stained the same as blood and selected fields appear as illustrations (Plate II).

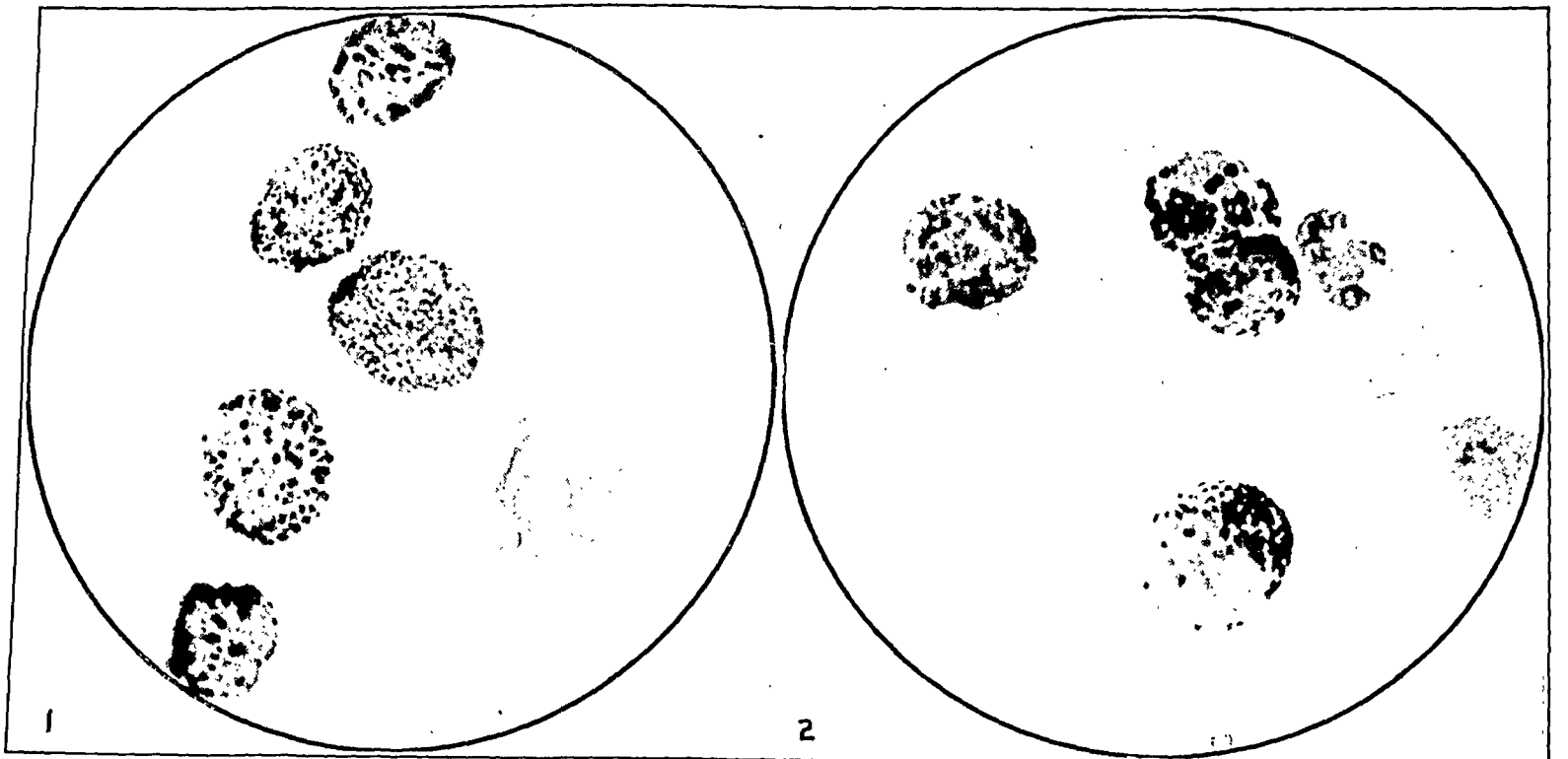
Autopsy smears of sternal marrow were stained as blood after first being extracted with ether and alcohol and typical fields appear as illustrations (Plate III).

We have been interested[12] in haploid mitotic figures in the type cell of various leukemias and have searched both blood and marrow smears of this case with diligence and found a total of 26, all in large non-granular cells such as appear in the various illustrations. A selection of these are to be found in Plate IV. So far as we could determine, many of these are haploid myeloblasts.

We find no mitotic figures in basophils. In all other cases where we have found haploid mitotic figures they have been in what would be considered the type cell of the leukemia and we have shown this.[12] We believe this to be confirmatory of the contention that a leukemic state is a type of malignant growth with immature, abnormal, imperfect cells proliferating without much differentiation.[12] Irregular mitotic division indicates cell abnormality and imperfection.

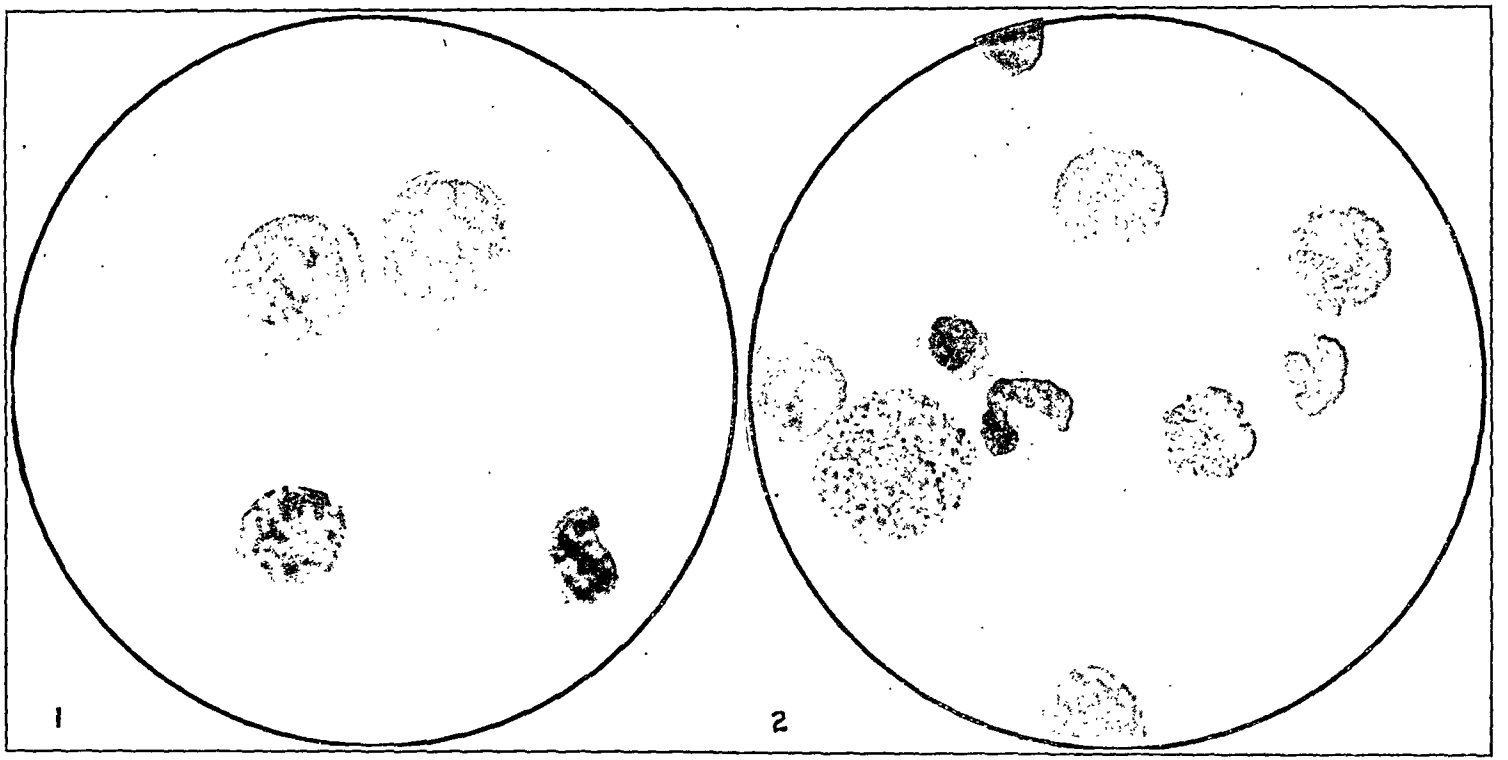
Discussion and Conclusions (Dr. Groat). We believe it important that the few reported cases of leukemia with true basophilic predominance have other common characteristics. It is also noteworthy that the few eosinophilic leukemias reported resemble each other and in certain respects resemble the basophilic cases. In the literature one finds a cautious attitude toward eosinophilic and basophilic leukemias. Practically everyone has mentioned the tendency for eosinophils and basophils to be increased in chronic myeloid leukemias. There are many cases in every hematologist's experience in which numerous basophilic and eosinophilic myelocytes and promyelocytes, and, or, plentiful mature looking mast cells and eosinophils are showy features in the stained film. They make Schilling's "gay picture." There is agreement that the basophils or eosinophils in what have been called special leukemia types keep toward the mature regardless of the company they keep. As in our case, one finds a gradual gradation of maturity so that division into classes is more or less arbitrary. We show a left shift in our case but do not confirm Sabrazès,[4] that the basophils may be traced back to the hemohistioblastic cell of Ferrata through the granular intermediate cell of Di Guglielmo.[7] We are quite familiar with these two cells, have photographed them, both in black and white and in natural color; they have been a part of our exhibits.[10,12]

The cytoplasm of these large sprawling, loosely flowing, Ferrata cells stains pale blue, the sparse granules and little rods gray violet, the large round loose-skeined nucleus pale magenta with our blood stain. The Di Guglielmo variant of this cell is smaller, more rounded, with cytoplasm more sharply defined. Either may con-



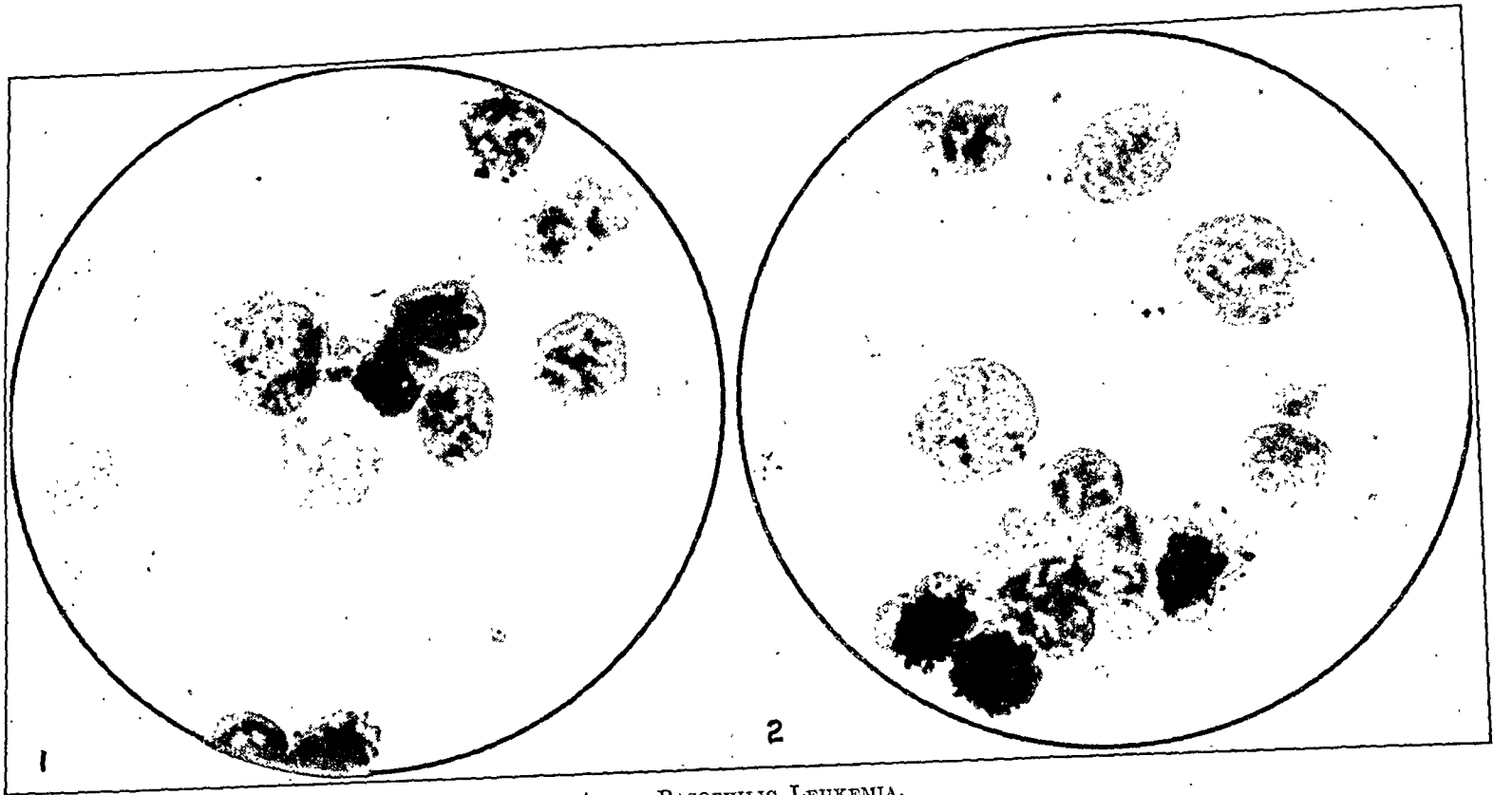
ACUTE BASOPHILIC LEUKEMIA.

PLATE I.—Photomicrographs × 1200, blood smears taken October 1, 1935, showing various types of basophilis (Miss Zimmer).



ACUTE BASOPHILIC LEUKEMIA.

PLATE II.—Photomicrographs × 1200, smears of sternal marrow obtained by biopsy October 1, 1935 (Miss Zimmer).



ACUTE BASOPHILIC LEUKEMIA.

PLATE III.—Photomicrographs × 1200, smears of sternal marrow obtained at autopsy October 5, 1935 (Miss Zimmer).

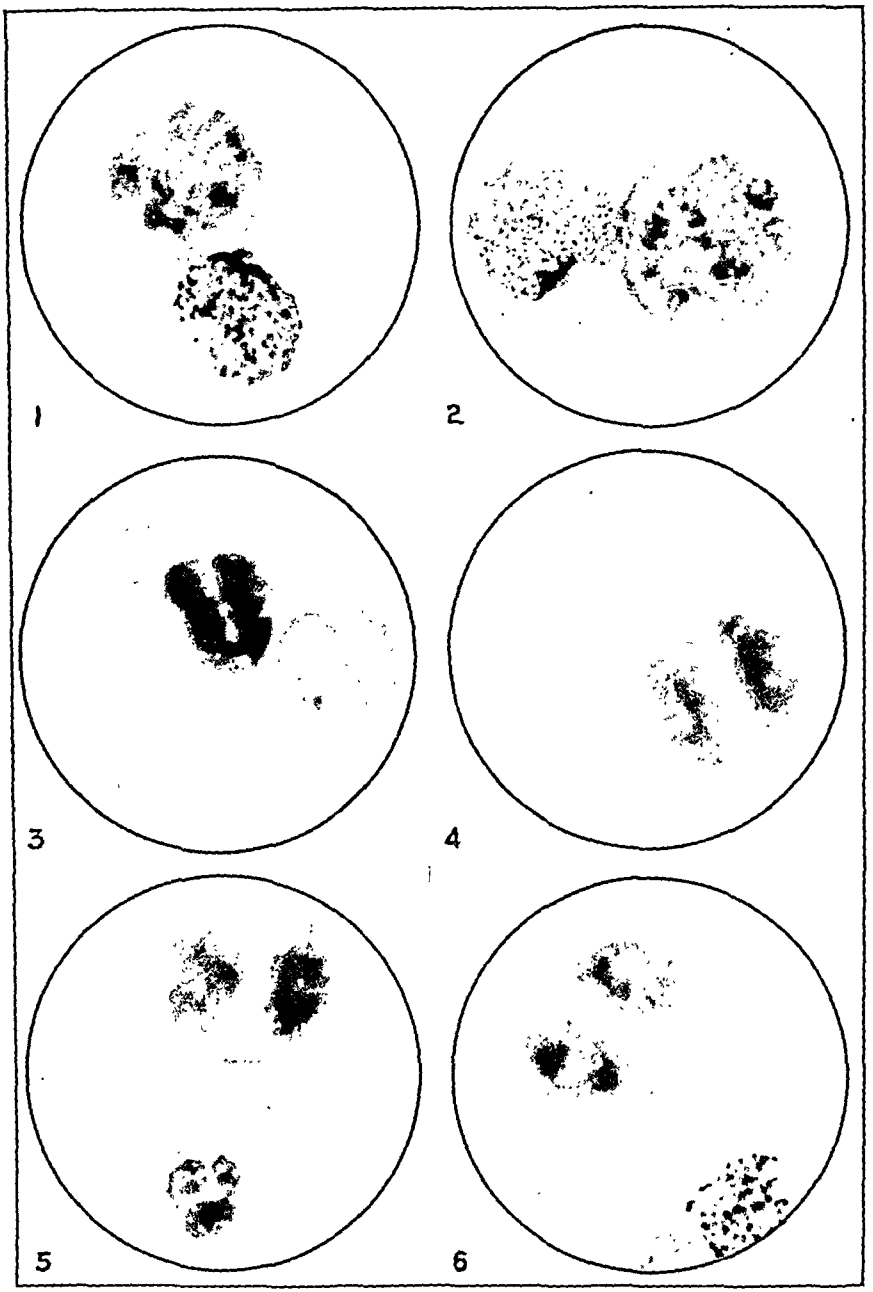


PLATE IV.—Various stages of mitotic division found in the large myeloblasts, all apparently haploids except No. 2 which may be diploid or multipolar.

tain particulate matter. We regard them as hematopoietic system cells; macrophages; clasmatocytes; possibly primitive monocytes.

Only one Ferrata cell has been found in this case notwithstanding thorough search for them. We know these cells but do not feel that Di Guglielmo[7] and Sabrazès[4] have established their point, that multipotent reticulo-endothelial cells build up azurophilic granules and rods with a nucleus of spongy reticular type with two or three nucleoli, to become the so-called hemohistioblasts of Ferrata and that these go to differentiate directly into basophilic mast cells. There is confusion caused by one thinking of the hemohistioblast solely as a blood cell while another speaks of it both as a blood and tissue cell. We are committed to the idea that blood cells found in adults are normally contained in a closed hematopoietic system which makes a special environment[11,12] to which they are suited.

Leaving the origin of the basophil and the reasons for its appearance as the predominating cell in a leukemia unexplained, the question remains, Is the basophil that is abundant in these reported cases the leukemia cell? In our case we believe it is not. We doubt whether it is in any of the cases, or that the eosinophilic cell found in the so-called eosinophilic leukemias is the leukemia cell. We do admit the possibility. There is much that indicates that others have been equally skeptical. We believe that in our study we have developed some evidence to show that the basophil is not the leukemia cell. In our case and possibly in other cases if they might be fully reviewed, if one could but remove the basophils from the picture, all the essential features of an acute myeloid leukemia would remain. We are aware of the limitations in the term "acute" in relation to leukemia. While acute myeloid leukemias are usually myeloblastic, they need not be. While acute leukemias usually run a short course, it has been customary to determine the beginning as the time when a definite illness and leukemia blood picture appear. We have been able to show, particularly in a series of leukemias in children which two of us (Wyatt and Groat) will soon report, that even this most acute type of leukemia may go for considerable time without obvious blood expression. The fact that Sabrazès' chronic case had an early less malignant phase followed by remission is not remarkable in a leukemia. We have subscribed to the idea that a preleukemic period probably always occurs,[12] and that a preliminary episode followed by a remission is by no means uncommon. In our study of leukemias in children soon to appear, one infant had an acute aleukemic episode, seemingly recovered, appeared well a year and then died with acute leukemia. Autopsy showed widespread leukemic infiltration.

Our finding of haploid mitotic figures only in myeloblasts identifies that cell type as the leukemia cell.[12] The presence of many

relatively mature basophils with an increasing left shift as the malady progresses may only indicate that for some unknown reason basophilic production has been unduly stimulated. We gain the impression that the large number of basophils is merely an exaggerated expression of what is commonly found in the myeloid leukemias. The fact that this case was carefully studied early by Dr. Pfotzer, and found to be a myeloid leukemia without basophilic increase, supports this contention. In the phase in which we saw the case, with a few noteworthy exceptions to which attention has been drawn, it is a counterpart of the reviewed cases, particularly that of Sabrazès.

We would like to call our case acute myeloblastic leukemia with extreme basophilia but believe the term "basophilic leukemia" should be retained until more complete evidence and confirmation has been presented. One may consider these numerous basophils as the progeny of the leukemia myeloblasts potentially basophilic. They are perhaps too evenly distributed along the ancestral line, too normal in appearance and too mature. There is no "hiatus" such as Naegeli speaks of, no gap. The hiatus is in the neutrophil line. The neutrophilic myelocytes are few and neutrophilic promyelocytes practically absent.

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THE RESISTANCE OF RETICULOCYTES TO HYPOTONIC SOLUTIONS OF SODIUM CHLORID AND OF PLASMA.*

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The variation from normal of the resistance of the red blood cells to hemolysis by hypotonic solutions in conditions in which the number of reticulocytes is increased has led to the belief that in this respect "reticulated" red cells differ from "non-reticulated" red cells. The literature contains many contradictory statements concerning the resistance of reticulocytes. By some authors[1,2,3] the resistance has been thought to be decreased; by others,[4,5,6,7] increased and by still others,[8,9,10,11] not to show any difference from that of adult cells. Such differences in resistance have been thought to be dependent on peculiar types of reticulocytes which appear in different abnormal states. Buckman and MacNaugher,[12] for example, found that reticulocytes from cases of pernicious anemia were less resistant to hypotonic salt solutions than the other cells, whereas those found as a result of hemorrhage were more resistant than the other cells.

The red cell resistance to hypotonic solutions of sodium chlorid in various blood disorders has been described in a previous paper.[13] In the present study the resistance in certain cases in which there was an increase of reticulocytes has been investigated. The conclusions have been derived from two types of experimental data: first, an analysis was made of the relation of the number of reticulocytes to the resistance of the red cells to hemolysis in 100 cases of anemia; second, the actual number of red cells and reticulocytes surviving in progressive dilutions of hypotonic sodium chlorid or plasma was determined in a few selected cases of anemia.

Methods. The resistance studies in hypotonic sodium chlorid were made according to the method recently described[13] in which a 0.1 cc. sample of a 20% suspension of washed red cells in 0.85% sodium chlorid solution was added to each of a graded series of 1 cc. samples of hypotonic sodium chlorid. For other resistance studies 1 cc. of a known suspension (30 or 40%) of red cells in plasma was added to each of a graded series of hypotonic plasma solutions. The plasma was rendered hypotonic by the addition of distilled water. In both methods, after thorough mixing, the tubes of cell suspension were allowed to stand for 1 hour. After a careful resuspen-

* This work was enabled in part by the Charles Sedgwick Minot Fellowship of Harvard University.

sion of the cells, red cell counts and reticulocyte preparations were taken from each tube in quick succession.

The red blood cell counts in the hypotonic sodium chlorid suspensions were made in white blood cell pipettes using dilutions of 1 to 20 or 1 to 10. For the plasma suspensions the counts were taken in red blood cell pipettes in dilutions of 1 to 100 or 1 to 200. The error due to the counting of the red cells and to distribution when such low values are obtained is comparatively large as has been determined previously.[14] The standard deviation, when two chambers of 5 squares each are counted, varies from ±60,000 for a count of 750,000 per c.mm. to ±108,000 for a count of 3,000,000. When the counts were in the vicinity of 100,000 or 150,000, as in the sodium chlorid suspensions, they were made in white blood cell pipettes and the standard deviations were ±7,000 and ±8,000, respectively.

Preparations for reticulocyte counts were made on cover slips upon which a drop of a 0.5% alcoholic solution of brilliant cresyl blue had evaporated to dryness. The dried blood films were counterstained with Wright's stain and at least 1000 red cells counted to determine the percentage of reticulocytes. The counting of reticulocytes on smears made from the more hypotonic solutions is difficult because of the presence among the other cells of shadow cells or hemolyzed cells. Only intact cells containing hemoglobin were counted whether reticulum appeared to be present or not. The standard deviation for one individual counting the reticulocytes (1000 red cells) in 10 consecutive smears taken on capillary blood of 1 patient was ±0.7% at a level of 10.5% reticulocytes. The standard deviation of counting the reticulocytes in 10 consecutive samples taken from a suspension of cells was ±2.6% with a count of 22% reticulocytes. The mixing of the sample introduces another error to the simple counting of reticulocytes.

Results. The results of 100 resistance observations are presented in Chart I. This group includes 38 observations in 19 cases of hypochromic anemia, 38 in 19 cases of pernicious anemia before treatment and in 2 cases during the response of the reticulocytes to potent therapy, and 24 in 15 cases of hereditary or acquired hemolytic jaundice. The absolute number of reticulocytes is plotted as abscissa against the minimum resistance or trace of hemolysis and against the maximum resistance or complete hemolysis as ordinate. Chart I shows no evident relation between the number of reticulocytes and the minimum or the maximum resistances, although the number of reticulocytes varied from normal values (under 50,000) to 800,000 per c.mm. If the reticulocytes were responsible for the decrease from the normal minimum or the increase from the normal maximum resistance some correlation should appear. Studies of this kind show no constant relationship between the number of reticulocytes and the resistance to hemolysis of the total cell population.

An attempt was made to determine whether the reticulocytes were more or less resistant than the red cells as a whole by determination of the relative proportion of reticulated and non-reticulated cells surviving in successive hypotonic solutions. The results of studies in hypotonic solutions of sodium chlorid are shown in Table 1 and those in hypotonic solutions of plasma, in Table 2.

The red cell resistance has been shown to vary at the time of a reticulocyte response. If the reticulocytes have the same resistance as the adult red cells, the percentage of reticulocytes should be constant in all the hypotonic solutions; if the reticulocytes are more resistant than the red cells, their percentage should be increased in the lower concentrations; and if the reticulocytes are less resistant than the red cells, their percentage should be decreased as the solutions become more hypotonic.

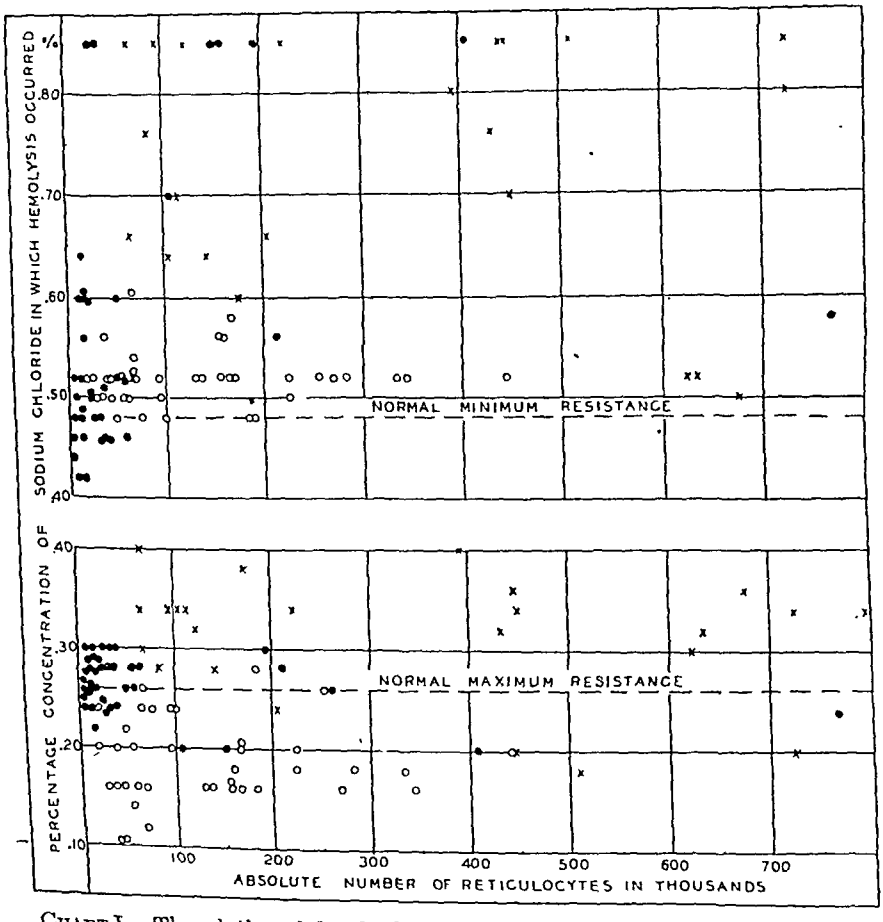


CHART I.—The relation of the absolute number of reticulocytes in 100 observations in anemia to the minimum resistance and maximum resistance of the red blood cells to hypotonic solutions of sodium chlorid.

× 24 observations in hereditary and acquired hemolytic jaundice.
• 38 observations in pernicious anemia.
° 38 observations in hypochromic anemia.

The cells of 3 cases of pernicious anemia (Table 1) were studied before, during, and after the response of the reticulocytes to potent therapy. In Case 1 the percentage of reticulocytes in the hypotonic solutions is practically constant at each of the 3 observations. In Case 2 the percentage of reticulocytes increased in the lower dilu-

tions in the first 2 of the 3 observations. In Case 3, the first observation showed a definite increase of the percentage of reticulocytes in the more hypotonic solutions, and the second observation only a moderate increase in their percentage. Therefore, in certain instances the reticulocytes during remission in pernicious anemia appear to be somewhat more resistant than the red cells as a whole. In the same patient, however, the reticulocytes are apparently more resistant at some times than at others. At times no demonstrable difference between the resistance of the reticulocytes and that of the total red blood cell population can be ascertained by this method.

TABLE 1.—COMPARATIVE RESISTANCE OF RED BLOOD CELLS AND RETICULOCYTES TO HYPOTONIC SOLUTIONS OF SODIUM CHLORID. THREE CASES OF PERNICIOUS ANEMIA.

CASE 1.

NaCl, %	Three Days Before Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	At Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	Three Days After Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %
0.85	0.118	13,216	11.2	0 161	...	..	0.111	9,768	8.8
0.80	0 117	...	..	0 172	41,624	24 2	0.112	10,080	9.0
0.70	0 124	...	.	0 177	49,206	27 8	0.128	...	..
0.60	0 127	...	..	0 163	50,204	30 8	0.115	9,430	8.2
0.50	0.127	16,830	13 2	0 126	27,216	21 6	0.137	10,960	8.0
0.40	0 080	13,524	16 8	0.101	28,684	28.4	0.053	4,399	8.3
0.36	0.046	7,636	16 6	0 052	15,600	30 0			

CASE 2.

	Two Days Before Peak of Reticulocyte Response.			At Peak of Reticulocyte Response.			Two Days After Peak of Reticulocyte Response.		
0.85	0.093	..	..	0 129	22,446	17.4	0.110	16,610	15.1
0.80	0.103	...	..	0.118	25,606	21.7	0.114	...	..
0.70	0.091	11,102	12.2	0 105	17,850	17.0	0.097	16,380	16.8
0.60	0.083	7,765	9.3	0 104	21,528	20.7	0.116	15,080	13.0
0.50	0.100	9,045	9 0	0 105	20,475	19.5	...	...	..
0.40	0.062	6,820	11.0	0 104	21,008	20.2	0.057	7,809	13.7
0.34	0.023	2,890	12.3	0.027	10,807	39.3	...	...	..
0.32	0.013	3,159	23.4						

CASE 3.

	Two Days Before Peak of Reticulocyte Response.			At Peak of Reticulocyte Response.		
0 85	0.141	12,690	9.0	0.118	17,736	15.2
0.80	0.140	...	..	0.102	20,196	19.8
0.70	0 125	17,000	13.6	0.104	19,760	19.0
0 60	0.134	16,080	12.0	0.106	20,908	19.8
0 50	0.119	15,232	12.8	...	...	..
0 40	0 107	15,408	14.4	0 094	14,776	15.4
0.36	0.033	8,710	26.0	0.039	6,630	17.0
0 32	0 017	5,678	33.4	0.019	4,446	23 4

In Table 2 are presented the results of determination of the reticulocyte resistance in various conditions with increased numbers of reticulocytes. In 3 observations on 2 cases of pernicious anemia the percentage of reticulocytes increased in the lower saline dilutions while in 2 other cases the percentage of reticulocytes was quite constant. These results suggest similar conclusions in regard to the resistance of reticulocytes to those drawn from the observations in Table 1.

Two sets of observations on the blood of a case of acquired hemolytic jaundice, which contained from 20 to 68% reticulocytes over a period of 4 months showed an opposite tendency. In both exper-

TABLE 2.—COMPARATIVE RESISTANCE OF RED BLOOD CELLS AND RETICULOCYTES TO HYPOTONIC SOLUTIONS OF PLASMA.

PERNICIOUS ANEMIA.

Hypotonic dilutions of plasma, c.c.	Case 1. At Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	Case 2. At Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	Case 3. Day Before Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	Case 3. At Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %	Case 4. Day Before Peak of Reticulocyte Response. R. B. C. in millions per c.mm.	Reticulocytes, per c.mm.	Reticulocytes, %
100	0.975	133,575	13.7	0.987	205,296	20.8	1.190	202,300	17.0	1.077	186,321	17.3	1.020	108,120	10.6
90	...		..	0.952	257,040	27.0	1.040	189,280	18.2	1.157	196,690	17.0	1.040	97,760	9.4
80	...		12.5	1.070	287,830	26.9	0.950	161,500	17.0	1.060	181,260	17.1	0.980	105,840	10.8
70	...		..	1.000	251,000	25.1	0.980	167,580	17.1	1.120	199,360	17.8	1.070	103,790	9.7
60	0.935	120,615	12.9	0.890	218,940	24.6	1.090	179,850	16.5	1.090	188,570	17.3	1.030	122,570	11.9
55	1.000	124,000	12.4	0.870	214,020	23.6	...		..	...		..	0.905	99,550	11.0
50	0.820	95,940	11.7	...		..	0.790	146,150	18.5	1.070	189,390	17.7	...		..
45	0.710	78,810	11.2	0.800	228,000	28.5	0.745	132,610	17.8	0.750	136,500	18.4	0.905	100,455	11.1
40	0.415	48,555	11.7	0.555	158,730	28.6	0.620	128,960	20.8	0.695	164,715	23.7	0.810	83,430	10.3
35	...		22.5	0.280	73,640	26.3	0.063	21,621	33.0	...		..	0.430	49,450	11.5

	ACQUIRED HEMOLYTIC JAUNDICE—CASE 1. April 20, 1934.			April 24, 1934.			HEREDITARY HEMOLYTIC JAUNDICE.			ARSENIC POISONING.		
100	0.840	287,280	34.2	1.120	462,560	41.3	...		..	1.330	53,200	4.0
80	0.920	306,360	33.3	1.180	443,680	37.6	1.680	149,520	8.9	1.250	51,250	3.0
70	...		..	0.785	306,935	39.1	...		..	...		..
60	0.710	230,040	32.4	0.985	308,305	31.3	1.860	161,820	8.7	1.350	62,100	4.6
55	...		..	...		..	1.760	183,040	10.4	...		..
50	0.592	121,360	20.5	0.660	201,300	30.5	1.685	190,485	11.3	1.110	45,510	4.1
45	0.152	25,773	16.9	...		..	1.560	176,280	11.3	0.867	36,414	4.2
40	0.045	5,220	11.6	0.135	30,240	22.4	0.770	67,760	8.8	0.565	27,120	4.8
35	...		..	...		..	...		..	0.235	9,165	3.9

	ERYTHROBLASTIC ANEMIA.			HYPOCHROMIC ANEMIA.			ACUTE BLOOD LOSS.			RABBIT 1. REPEATED BLOOD LOSS.			RABBIT 2. REPEATED BLOOD LOSS.		
100	2.780	230,740	8.3	2.170	235,445	10.8	...		..	1.270	158,750	12.5	1.400	145,600	10.4
90	...		..	...		..	...		..	1.380	171,120	12.4	...		..
80	2.940	255,780	8.7	2.020	208,060	10.3	...		..	1.580	199,080	12.6	1.220	120,780	9.9
70	2.680	233,160	8.7	...		..	...		..	1.320	142,560	10.8	...		..
60	2.320	160,080	6.9	2.315	203,720	8.8	...		4.8	1.400	147,000	10.5	1.380	139,380	10.1
55	...		..	...		..	...		..	1.400	179,200	12.8	...		..
50	2.070	184,230	8.9	1.745	148,320	8.5	2.090	89,000	4.3	1.295	175,000	14.0	1.240	128,960	10.4
45	...		..	...		..	...		..	0.825	100,650	12.2	0.875	87,500	10.0
40	1.935	150,930	7.8	1.255	99,145	7.9	1.125	36,000	3.2	0.552	71,760	13.0	0.095	11,495	12.1
35	1.350	116,100	8.6	0.700	52,500	7.5	0.850	34,000	4.0	0.095	11,020	11.6	0.047		..
30	1.195	109,940	9.2	0.170	21,250	12.5	0.570	21,660	3.8	...		..	...		..
25	1.100		..	...		..	0.245	6,860	2.8	...		..	...		..

iments the percentage of reticulocytes was very definitely decreased in the more hypotonic solutions, *i. e.*, they were less resistant than the red blood cell population as a whole.

In 1 case each of hereditary hemolytic jaundice, arsenic poisoning, erythroblastic (Cooley's) anemia, hypochromic anemia, and acute blood loss, and in 2 examples of repeated blood loss in rabbits the percentage of reticulocytes remained quite constant in the lower dilutions of hypotonic plasma. Apparently there was no striking difference between the resistance of the reticulocytes and that of non-reticulated cells in this last group of cases studied.

Discussion. There are many sources of error in counting reticulocytes in hypotonic solution which may be responsible for the divergent results of many investigators. When hemoglobin is removed from the red cell by hemolysis a shell or shadow form remains. The reticulum-like material, stained with brilliant cresyl blue, persists, so that the first impression in looking at the cells in the sediments of hemolyzed blood is that none of the reticulocytes has been hemolyzed. This may account for the conclusions in the early work of Chauffard and Fiessinger[15] that reticulocytes were more resistant than the other cells.

Key[10] pointed out that the laked cells floated above the non-laked cells in the sediments in hypotonic solutions. Sampling the top layer, he indicated, might have led to the erroneous conclusion of certain investigators that the reticulocytes were more resistant than non-reticulocytes. When the sediments were thoroughly mixed no constant difference could be observed between reticulocytes and non-reticulocytes in respect to their resistance.

Some investigators[7] have employed a method in which salt solutions containing cresyl blue in solution were used. With "high dry" magnification or in fresh preparations, it is difficult to distinguish in the counting chamber the reticulocytes that have been laked from those that have retained their hemoglobin. Moreover, the oldest reticulocytes, which have only a small amount of punctate reticulum[16] cannot be discerned under "high dry" power and therefore a smaller number of reticulocytes is counted than is actually present.

Buckman and McNaugher[12] report experiments with defibrinated blood incubated at 37° C. for 12 hours. The decrease in the number of reticulocytes at the end of 12 hours, which is interpreted as evidence of decreased cell resistance, is no more than could be expected by the normal maturation of these young cells.[16]

Many conclusions in regard to the resistance of red cells have been drawn from the coincident occurrence of reticulocytes and diminished resistance or increased resistance to hemolysis. The early work of Chauffard[1] assumed that since reticulocytes were increased and resistance was decreased in hemolytic jaundice there was a relationship. Cathala and Daunay[2] found increased reticulocyte counts and diminished resistance of red cells in infants at

birth, and came to similar conclusions. Other observers correlated increased resistance of the red blood cells with the increase of reticulocytes after repeated venesections.[4,5]

Meulengracht[11] concluded from microscopic studies of reticulocytes in fresh preparations from the blood of patients with hemolytic jaundice that there was no relation between the number of reticulocytes and the red cell resistance.

It has been shown[13] that alteration of both maximum and minimum resistance may take place simultaneously in the same patient at the time of a reticulocyte response to either iron or liver therapy. This alteration, however, may be due to factors not necessarily confined to the reticulocytes. Changes in hemoglobin content, volume of cells, and shape of the cells are known to take place at this time, as well as chemical and physical factors which are less easy to measure. Thus the heterogeneity of the cell population is increased not only in respect to age but also in respect to the physical and chemical properties of the cells. In experimental and clinical hypochromic anemia, the volume, thickness and hemoglobin content of the cells are decreased. Under these circumstances, regeneration of blood in response to iron therapy may be accompanied by the appearance of reticulocytes which contain less than normal amounts of hemoglobin. On the other hand, reticulocytes in some conditions, such as hereditary hemolytic jaundice, may be small and full of hemoglobin. Thus differences in resistance of reticulocytes do not seem to be due to any property peculiar to the reticulocytes as such (*e. g.*, because they are young cells), but may be due to fundamental changes in the hemopoietic system during regeneration of blood which may at times affect mature cells as well as immature cells.

Conclusions. 1. The absolute number of reticulocytes observed in 100 cases of pernicious anemia, hypochromic anemia, and hereditary or acquired hemolytic jaundice showed no consistent effect in altering the minimum resistance or maximum resistance of the total red blood cell population to hypotonic sodium chlorid solutions.

2. Actual enumeration of the relative numbers of reticulocytes and red cells surviving in progressive series of hypotonic solutions of sodium chlorid and of plasma showed that, irrespective of the disease present, in some bloods the reticulocytes were more resistant, in some equally resistant, and in some less resistant than the red blood cell population as a whole in the cases studied.

3. Reticulocytes as well as non-reticulocytes vary in age, volume, thickness, hemoglobin content, and probably other physical and chemical properties in the same individual at different times, and in different individuals with varied disease conditions. Thus the fact that young cells are reticulocytes does not necessarily determine their behavior in hypotonic solutions. The reticulocytes may or may not exhibit divergence from the resistance of the cell population as a whole. Such variations may be responsible for the diverse

opinions of other observers in regard to the resistance of reticulocytes to hypotonic solutions of sodium chlorid and plasma.

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SICKLE-CELL ANEMIA: A NEW CAUSE OF COR PULMONALE.

REPORT OF TWO CASES WITH NUMEROUS DISSEMINATED OCCLUSIONS OF THE SMALL PULMONARY ARTERIES.

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THE history of joint pains, with or without fever, the presence of an enlarged heart, the finding of a systolic precordial or mitral murmur and the discovery of enlargement of the liver frequently

lead to the diagnosis of rheumatic heart disease in cases of sickle-cell anemia. According to Anderson and Ware a cardiac murmur is present in 75% of the cases, enlargement of the liver clinically in 53% and enlargement of the heart clinically in 48%. Joint pains occur at some time, often intermittently, in 51%. Dyspnea, however, is usually not a prominent symptom, but it is common experience that effort dyspnea is difficult to elicit in the histories of many Negro cardiac patients. Hamman has reported an interesting case of a Negro girl with sickle-cell anemia in which several excellent clinicians made the diagnosis of rheumatic heart disease, with failure, which was not verified by necropsy. Diggs and Ching state that "Clinically, organic heart disease is often suspected, but at autopsy there are no constant cardiac changes except those explainable on the basis of anemia. The heart is moderately enlarged, the myocardium pale and flabby. On microscopic examination fatty degeneration and moderate scarring are noted." These authors and Steinberg note that the liver is consistently moderately enlarged and the sinusoids distended with varying amounts of blood and that the lining endothelial cells frequently contain brown granules, good evidence of congestion as well as blood destruction.

Although many patients with sickle-cell anemia die at a relatively early age of some intercurrent infection, particularly pneumonia and pulmonary tuberculosis, a fair number die apparently as the result of the anemia itself. It is our belief that cardiac failure is often a part of the terminal picture, as evidenced by enlargement and dilatation of the heart and passive congestion of the liver. Our experience with 2 cases leads us to believe that there is usually something other than the severe anemia producing the cardiac failure, namely, hypertension of the lesser circulation due to numerous occlusions of the medium-sized and small pulmonary arteries with subsequent hypertrophy and failure of the right heart.

Case Reports. CASE 1.—H. P., a Negro woman, aged 38 (?), entered the Georgetown University Hospital on February 19, 1935, complaining of dyspnea and swelling of the abdomen. She had attended the Out-Patient Department from August 13, 1934, to October 20, 1934. During that period of observation she had had no definite complaints—was merely not feeling well. She had had attacks of numbness of the feet and pains in the legs, but these had not occurred for several months. She did not recall any previous illnesses except ulcers of the legs some 10 years before which had healed after a long time. Menstruation had begun at the age of 12 years and had been regular but scanty until 3 years before, when it had ceased. She had been married 5 years but had never been pregnant. There was moderate leukorrhea. There were no cardiovascular, respiratory, urinary or other functional disturbances, except "eye strain," for which she had received treatment at the Episcopal Eye, Ear, Nose and Throat Hospital. Physical examination in the Out-Patient Department had been negative except for conjunctival pallor; bad dental condition; a firm, diffuse, freely movable mass in the right breast and smaller discrete masses in the left breast; a systolic apical murmur and a questionable presystolic rumble. The blood pressure had been 120 systolic and 80 diastolic. Urinalysis

showed 1+ albumin and 3+ leukocytes. Wassermann and Kahn tests of the blood were negative. The hemoglobin was 54% (Sahli method), the erythrocytes numbered 1,850,000 per c.mm. of blood and the white blood cells 8200. There was great variation in the size and shape of the erythrocytes but there were no definitely sickle-shaped cells in the fresh smear. After incubation of a wet smear overnight there were numerous fusiform, stellate-shaped and sickle-shaped erythrocytes characteristic of sickle-cell anemia. The patient was urged repeatedly to enter the hospital but would not do so until the onset of the final episode of her life.

On admission to the hospital the patient stated that 3 days before severe dyspnea had begun, associated with swelling of the abdomen. Both symptoms progressed rapidly.

Physical examination revealed a well developed and nourished orthopneic Negress. The ocular fundi were essentially normal. The conjunctivæ and buccal mucous membranes were pale. Cyanosis was not present. There was much dental work and some pyorrhea. The cervical veins were markedly distended, pulsated and filled from below as well as from above. The breasts contained the masses already noted, but the large one in the right breast was now fixed to the skin and the nipple was retracted. Moderately enlarged, firm lymph nodes were palpable in the right axilla. There was dullness in the right hemithorax posteriorly up to the fourth interspace. The breath sounds were exaggerated in the interscapular space. There were no râles. The point of maximum intensity of the apex beat was easily determined to be in the sixth interspace, 11 cm. to the left of the midsternal line (clavicle, 15 cm.). There was a harsh systolic murmur over the precordium, loudest at the apex, and a questionable diastolic murmur at the apex. The heart shifted with change of position. The rhythm was regular and the rate 100 beats per minute. The blood pressure was 105 systolic and 60 diastolic. The abdomen was very prominent in its upper portion, due to great enlargement of both lobes of the liver, which extended about 7.5 cm. below the costal margins. There was apparently no ascites. There was no edema of the legs. Ulcers were noted on both legs. The temperature was 100° F.

The hemoglobin was 52% (Newcomer method), the erythrocytes numbered 2,500,000 per c.mm. of blood and the white blood cells 11,400, with 86% neutrophils. There was marked anisocytosis and poikilocytosis. Urinalysis showed 4+ albumin and 2+ hyalin casts. A roentgenogram showed great enlargement of the heart, both to the right and left, with a bulge in the region of the pulmonary conus and widening of the superior mediastinal shadow on the right and left, due apparently to engorgement of the great veins. There was some mottling of the lung fields, suggesting mild congestion (Fig. 1).

The temperature dropped to normal and remained so. The pulse rate became stabilized at 90 beats per minute. The orthopnea continued. Subcrepitant râles appeared at the bases of both lungs posteriorly. On the night of February 21 the patient became wildly excited and complained of great pain in the sacral region and some in the lower abdomen, relieved by a hypodermic injection of morphin sulphate, 0.011 gm. ($\frac{1}{6}$ grain). The blood pressure at this time was 100 systolic and 50 diastolic. Slight edema of the ankles developed. Death occurred at 7.40 A.M., February 22, 1935, 66 hours after admission and 5 days after the apparent onset of the right heart failure.

Necropsy Report. The postmortem examination was performed by Dr. Hansmann on the unembalmed body, the same day at 11.00 A.M. The body was that of a well developed and nourished Negress, 155 cm. in length, with delicate tapering hands and feet. There was no rigor. The eyes were prominent and practically protruded from the sockets. The small venules

of the conjunctivæ and scleræ stood out prominently, giving these structures a dusky appearance upon a yellowish background. The pupils were round and equal and measured 0.4 cm. in diameter. The conjunctivæ, nail beds and mucous membranes were cyanosed and icteroid. The veins of the neck were markedly distended, even the small veins of the scalp standing out prominently. There was no demonstrable edema. There were chronic ulcers laterally over the left ankle and over the right tibia. The right nipple was fixed to the underlying breast, and the breast, which was firmer than normal, was fixed to the underlying structures. The skin about the nipple was thickened and wrinkled and contained a few miliary nodules. The right upper quadrant was particularly hard and a poorly defined mass was felt. The right axillary lymph nodes were hard and enlarged up to 1.5 cm. Section of these structures revealed gray granular tissue characteristic of carcinoma. The left breast was uniformly firm. Cut section revealed resilient white scar tissue and a few cysts 1 cm. in diameter containing a bluish fluid. The left axillary lymph nodes were enlarged up to twice normal size but were not hard. The fat over the chest and abdomen was very edematous and measured 0.75 cm. and 3 cm. in thickness respectively.

On opening the thorax and abdomen, the serous cavities, with the exception of the left pleural cavity, were found to contain an excess of watery fluid. The pericardial cavity contained about 100 cc., the right pleural cavity about 200 cc., and the peritoneal cavity about 500 cc. The omentum was adherent to the anterior abdominal wall. The uterus, tubes and ovaries were infantile.

The mediastinum was markedly widened by a heart that was much more dilated than hypertrophied. It pushed the lungs aside. The right auricle participated in this widening of the mediastinum quite as much as the ventricles, and the right lung was obscured as much as the left. The superior and inferior venæ cavæ were markedly dilated. The opened heart, free of all blood clot, weighed 350 gm. The left ventricle was slightly dilated and hypertrophied. The right ventricle was very much dilated and hypertrophied, its wall measuring 0.4 cm., while that of the left measured only 1.2 cm. More important than these measurements was the tremendous thickening of the intracardiac muscle structures. They gave the interior of the heart a coarse, trabeculated appearance. The pulmonary valve orifice was about 1 cm. larger than normal in circumference. Other valve orifices appeared unaffected. The musculature of the right auricle was somewhat hypertrophied, especially when one considered the marked increase in the size of the cavity. The aorta contained a few young atheromatous plaques. The main pulmonary arteries were smooth, and the coronary arteries were apparently normal.

The lungs were edematous, and there was definite bleeding into the alveoli of the lower lobes. There was no gross area of infarction. When the lungs were sectioned, however, many thrombi in various stages of organization were seen in the small and medium-sized arteries. These vessels were evidenced by firm cylindrical structures from 1 to 2 mm. in diameter which varied from granular recent red blood clot to the pearly white glistening appearance of a fully organized thrombus. An individual thrombus involved several millimeters of a vessel that appeared normal elsewhere. This process was diffusely scattered throughout all lobes. The obstruction offered by these thrombi must have been great when one considered the facts that many occurred in a single section and that the length of the individual thrombi was but a few millimeters.

The spleen was markedly contracted and finely granular. The surface was reddish-white. It weighed 7 gm. On cut section the pulp was very gritty and had a distinct reddish appearance. The vessels entering and leaving the spleen were normal in size.

The gastro-intestinal tract showed definite edema. The liver weighed 1715 gm. It was acutely swollen, and the margins were blunted. Its color was deep blue streaked with yellow. The cut surface revealed opaque areas stained yellow in the location of the central veins. This indicated extensive central necrosis with dead cells stained with bile. The gall bladder was shrunken and thickened, and the cavity contained many pigment stones.

The right kidney weighed 200 gm, and the left 210 gm. They were somewhat globular, firm and red from passive congestion. The cut surface showed shrunken areas with underlying scars having the configuration of ancient small infarctions. The intervening kidney cortex appeared normal except that the glomeruli were about twice normal size and intensely congested. Near the apex of the pyramids the renal substance had a white glistening appearance which had the toughness of scar tissue. There was no visible atheroma of the larger arteries, but there was some thickening of the smaller arteries. The adrenals were normal in size and architecture. The urinary bladder was normal.

The brain weighed 1365 gm. The surface appeared normal grossly except that there had been some recent diapedesis of red blood cells into the meninges over the right hemisphere. Coronal sections were made. There was a small area of softening 1 cm. in diameter in the left parietal cortex. The choroid plexus was uniformly shrunken, ashen in color and in places appeared as a white cord. Upon exposing the spinal canal, a fibrinous plaque 1 cm. in diameter was noted upon the dura in the lumbar region posteriorly. Gross serial sections of the cord revealed small petechiæ in the nerve trunks as they emerged from the cord to enter the dorsal root ganglia in the dorsal and lumbar regions. The posterior root ganglia appeared normal. The pituitary gland was not abnormal.

The bone marrow from the upper one-fourth of the femur was gelatinous and had the appearance of edematous fat. It was distinctly gritty and necessitated decalcification before a section could be made.

Microscopic examination of the formalin-fixed tissues revealed the following: The muscle fibers of the myocardium were fragmented and somewhat granular. Some of the very thin-walled vessels were distended, giving the appearance of pools of blood. The smaller arteries were definitely tortuous and the walls were hyalinized. The knuckling of these vessels caused the vessel to be cut across as many as 4 times in the same plane.

Six sections taken from various parts of the lungs were studied. All showed occlusion of small arteries which had been stretched before they became occluded. The occlusions varied from recent thrombi to completely organized and canalized thrombi (Fig. 2, 3, 4, 5). Some small arterioles were thickened and hyalinized, while others were tremendously dilated and distended with blood. The alveolar walls were markedly lengthened, due to the extreme stretching of their capillaries by erythrocytes. The parenchyma had the appearance of most extreme passive congestion. Many areas appeared angiomatous because of the frequent cross section of lengthened snarled capillaries. The red blood cells contained in these vessels had a bizarre appearance. The characteristic forms were very long and had a digital arrangement. Many times the space between these elongated parallel cells was obscured and the appearance was then that of a hyalin thrombus of capillary size. A few of the thickened arteries had collections of hemosiderin in their walls, the consequence of old small hemorrhages. There were 3 small areas of recent infarction.

Section of the spleen necessitated decalcification. The section revealed a mass of hyalinized scar tissue which contained many occluded large and medium-sized arteries. There was still some of the intense blue color in the walls of some of the vessels characteristic of calcium incrustation. The

few vessels which had remained patent were closely packed with cells of almost every shape described in sickle-cell anemia.

Four sections of the liver were studied. The liver cords were markedly thinned. The sinusoidal spaces were dilated. Large areas appeared as a cavernous angioma filled with sickle cells, the intervening liver cells having disappeared from pressure atrophy. A large area about the central vein showed marked hepatic-cell injury and necrosis. The dead liver cells were hyalin. Neutrophils were in abundance digesting the dead cells. Injured cells were swollen and vacuolated. Small bile ducts were plugged with inspissated bile. There was abundant hemosiderin pigment in both the hepatic and Kupffer cells. Vessels entering the lobule from the periportal space were tortuous. No intact red blood cells were seen within Kupffer cells.

The pancreas was normal.

The kidneys were markedly diseased. Fourteen sections were studied from various parts. Near the apex of the pyramids and extending quite deeply into the kidney substance were plaques of dense hyalin scar tissue which appeared like cartilage. The rich network of capillaries had been destroyed, and the tubules traversing the scar had atrophied. The glomeruli were large and distended with sickle cells. Some of the cells were so closely packed that they appeared agglutinated and resembled hyalin thrombi. Small granules of hemosiderin were numerous in the endothelium of the glomerular tufts. There were many scars in the cortex. Many glomeruli were partially and completely sclerosed. Arterioles entering these areas were thickened and tortuous. The sclerosed glomeruli frequently had streaks of hemosiderin in them. It appeared that the glomeruli had become sclerosed while they were distended with blood. The lining cells of the convoluted tubules contained a great deal of hemosiderin.

Section of the breast revealed a scirrhous carcinoma, and the lymph nodes in the axilla were replaced by a mass of medullary glandular epithelial tissue. The lymph nodes from the bifurcation of the trachea were tuberculous. The axillary lymph nodes from the left axilla were hyperplastic. The endothelial cells of the sinuses contained hemosiderin, but no intact phagocytosed sickle cells were seen.

The bone marrow was made up largely of hyalin connective tissue similar to that seen in the kidney and spleen. It was necessary to decalcify this tissue before a section could be made. The section contained only a few small spicules of bone. It would appear that most of the calcium which the fresh tissue contained was incrusted calcium rather than calcium laid down in bone matrix in the normal process of ossification. Along one margin was a thin staff of active bone marrow. Between the hematopoietic cells were large pools of sickled cells.

A section of the aorta appeared normal.

The cortex of the brain revealed meningeal vessels distended with blood. A few sections showed a thin layer of diapedesed blood over the surface of the cortex. The vessels were so tortuous that as many as 8 cross sections of the same vessel were seen in a single space. Two vessels had many phagocytes filled with hemosiderin about them. There was 1 small area of recent softening. In the marginal zone of the cortex were many large mononuclear cells filled with a reddish-brown pigment. The choroid plexus was practically sclerosed and was markedly incrusted with calcium (Fig. 6). The lesion here was similar to the lesion in the spleen. The pituitary gland appeared normal. The cord showed a small hemorrhage into the meninges in the lumbar region. A nerve cell in the anterior horn was in the process of degeneration. About it was an area of edema and hemorrhage. The cord contained diffusely an unusual number of corpora amylacea, which were particularly numerous in the posterior

columns. There was an area of hemorrhage on the inner surface of the dura. The vessels in the nerve trunks were packed with sickle cells.

In view of the interesting findings in Case 1, and recalling the enlargement of the liver in the case previously reported by Yater and Mollari, we reviewed that case from the standpoint of pulmonary vascular lesions and the right side of the heart. A brief abstract of the history follows.

CASE 2.—S. C., a Negro woman, aged 25, entered Georgetown University Hospital on November 18, 1929, because of severe pains in both legs. She was about 6 months' pregnant. She had had these pains in the legs intermittently since early childhood. At the age of 14 she had been operated on in the hospital for an "osteomyelitis" of the distal third of the left tibia. Two years before she had entered the hospital because of bleeding following a miscarriage at 6 months. At this time she was very ill and had a septic temperature for 7 weeks. Her hemoglobin went as low as 12%, with 950,000 erythrocytes per c.mm. Following this illness she had never been strong and was always dyspneic on exertion.

On the last admission her temperature was 101° F., and the pulse 120 per minute. The blood pressure was 115 systolic and 65 diastolic. The heart was slightly enlarged to the left, the apex beat was diffuse, and a soft systolic murmur was heard at the apex. The liver was not palpable. There was no evidence of congestion. Blood examination showed 44% hemoglobin (Dare method), 2,570,000 erythrocytes per c.mm., and 14,800 white blood cells per c.mm. Sickling was seen in fresh smears. Wassermann and Kahn tests of the blood were negative. The electrocardiogram showed only sinus tachycardia.

The patient was in the hospital 6½ weeks until her death, with practically continuous and excruciating pains in the legs. The temperature fluctuated, but usually each day it rose to a point never over 101° F. The pulse rate varied continuously between 100 and 140 beats per minute. After 3½ weeks the patient miscarried spontaneously. Eighteen hours before death she suddenly vomited and began to complain of severe pain in the right side of the abdomen anteriorly and mainly in the region of the liver. A resistance was felt in the upper half of the abdomen suggestive of enlargement of the liver, which had not previously been noted. The pain continued until death, the pulse rate and temperature steadily falling.

Necropsy Report. There was edema, Grade 2, over the tibias. Cyanosis was not present. A small amount of clear, straw-colored fluid escaped when the abdominal cavity was opened. The liver was seen to fill the whole upper half of the abdomen, reaching below the costal margin in the right midclavicular line 14.5 cm., in the left midclavicular line 12 cm., and in the median line 18.5 cm. below the tip of the xiphoid process.

The pericardial sac measured 15.5 cm. in its transverse diameter and contained about 125 cc. of clear, straw-colored fluid. The heart weighed 379 gm. All cavities were distended with blood. The right ventricle was dilated Grade 3, the left Grade 2. The tricuspid orifice admitted 4 fingers, the mitral orifice 3. The right ventricle was definitely hypertrophied. The thickness of the left ventricle was 1.2 cm. in its mid portion, the right 0.55 cm. The muscle was reddish-brown and fairly firm. The endocardium and valves appeared normal. The aortic orifice measured 5 cm. in circumference, the pulmonic 7 cm. The coronary arteries were soft.

The lungs were emphysematous, Grade 2, in both upper lobes. Nothing otherwise notable was recorded except an area of bronchiectasis. They were not saved.

The spleen weighed 35 gm. and was typical of advanced sickle-cell anemia.



FIG. 1.—Case 1. Greatly enlarged heart with bulge in the region of the pulmonary artery and widening of the superior mediastinal shadow due to venous engorgement.

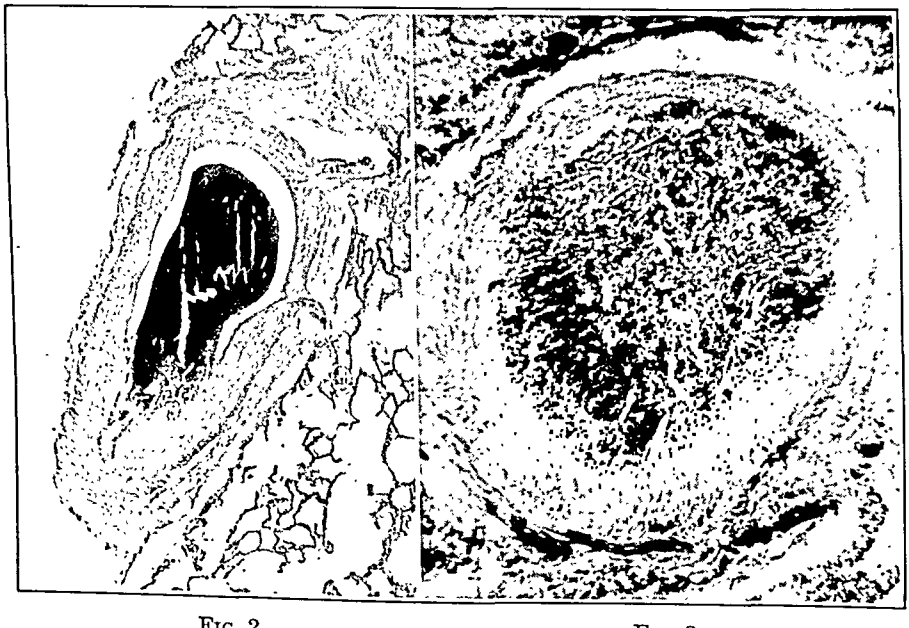


FIG. 2

FIG. 3

FIG. 2.—Case 1. A medium-sized pulmonary artery containing a recent thrombus which is undergoing organization at one point. (× 70.)

FIG. 3.—Case 1. A small pulmonary artery filled with an organized thrombus. (× 215.)



FIG. 4 FIG. 5

FIG. 4.—Case 1. A small pulmonary artery completely recanalized. (× 170.)
FIG. 5.—Case 1. Cross sections of a small recanalized pulmonary artery. (× 105.)

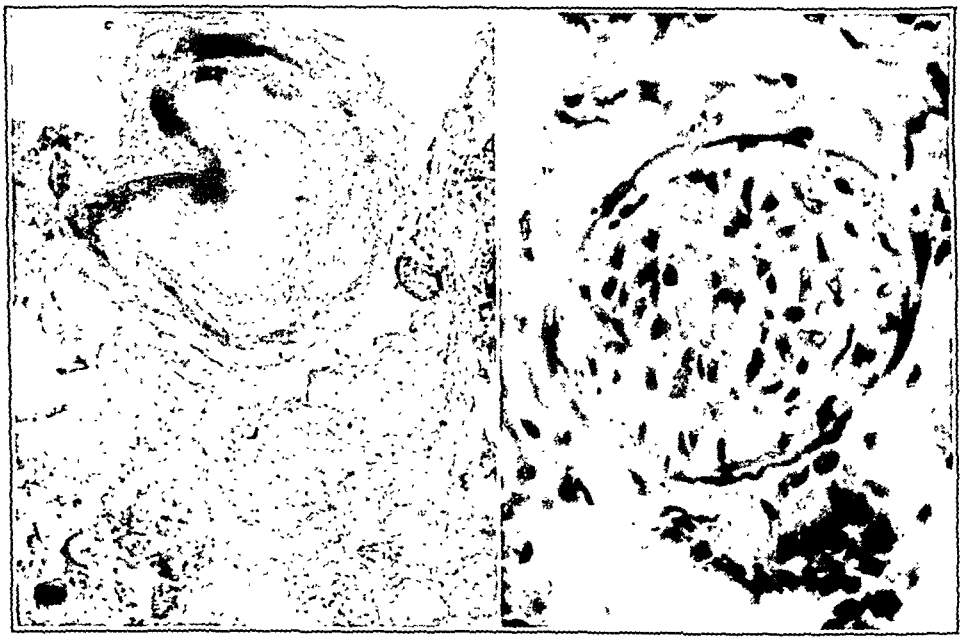


FIG. 6 FIG. 7

FIG. 6.—Case 1. Sclerotic choroid plexus with calcium incrustations. (× 135.)
FIG. 7.—Case 2. A representative arteriole in the lung with a greatly thickened wall, early degenerative changes and a small lumen. (× 1050.)

The liver weighed 2090 gm. It was reddish-brown with distinct yellow mottling throughout. The large veins were entirely empty, but dark clots filled many of the bloodvessels and were practically extruded when the cut was made. The gastro-intestinal tract was not remarkable.

The kidneys presented the same appearance as those of Case 1, but contained some fresh infarcts.

Microscopic examination showed engorgement of the capillaries of all of the organs. The spleen as previously described was the typical spleen of advanced sickle-cell anemia.

The myocardium showed fragmentation of the fibers.

The cords of liver cells were narrower than normal, and the sinuses were distended and in general filled with sickle-shaped erythrocytes. The picture was that of severe congestion. There were small "pools of blood" here and there. A more complete description appears in the report of Yater and Mollari.

The kidneys were similar to those of Case 1.

There was only one section of the lung. This showed engorgement of the capillaries of the alveolar walls, but most interesting were the arteries and arterioles. The medium-sized and small arteries had greatly thickened walls and were apparently quite tortuous. There were no old or recent thrombi in the section, nor was there clear cut evidence of ancient organization and canalization. The arterioles presented the appearance as seen in the arterioles of the kidneys in essential hypertension. There was great hypertrophy of the media with early degenerative changes. The lumens were greatly reduced in diameter (Fig. 7).

In Case 1 the histologic appearance of the medium-sized and small pulmonary arteries was suggestive of non-inflammatory thrombo-angiitis obliterans. Many of the vessels had been the site of a patchy thrombosis which had led to organization and recanalization. Others were in various stages of organization. Many fresh thrombi were present, and it was probably the sudden occurrence of these which caused the right ventricle, already working against obstruction in the pulmonary arterial tree, to fail entirely. We felt that the thrombotic phenomena and their sequelæ of organization and canalization were features of sickle-cell anemia, and our conviction was verified by the discovery of vascular changes in the lungs of Case 2.

In Case 2, although in the tissue material available there were no pulmonary arteries which contained fresh or organizing thrombi, the medium-sized and small arteries showed evidence of ancient changes which were probably due to thrombosis and organization. The arterioles all showed great medial hypertrophy and diminution in the diameter of their lumens. These arteriolar changes were probably secondary to the hypertension in the pulmonary circulation resulting from the obstruction in the medium-sized and small arteries, and may have represented compensatory changes to prevent overdistention of the arterioles. The arterioles were similar to those in the lungs of 2 cases described by Yater and Constam in which sickle-cell anemia did not exist.

In the original report of Yater and Mollari of Case 2 note was not made of the pulmonary vascular changes nor of the hypertrophy

of the right ventricle. The former were recorded in the original protocol but were not regarded as of sufficient importance to comment upon in the published report. The hypertrophy of the right ventricle was overlooked. We feel that the splenic lesions in sickle-cell anemia have been overemphasized and that other authors may have also been overlooking the pulmonary and cardiac lesions.

Cyanosis was not observed during life in either of the cases here reported. In this respect the cases did not present the typical picture of right heart failure known as Ayerza's syndrome. There is a striking difference, however, between the ordinary case of Ayerza's syndrome and the cardiac picture in sickle-cell anemia, namely, that in the one there is polycythemia and in the other usually severe anemia. Also, the usual case of cor pulmonale due to pulmonary arteriolar sclerosis is one in which dyspnea has occurred for months or years before death. The patient with severe sickle-cell anemia, however, dies usually before he can develop the full-blown picture of chronic right heart failure.

In reviewing the literature on the pathology of sickle-cell anemia we find reference by Steinberg to "marked congestion of the capillaries and the larger vessels (of the lungs) and the presence of serum in some alveoli" as constant observations in 5 cases in which descriptions of the lungs, free of pneumonia or tuberculosis, were given. Steinberg states that "In my patient, the small and medium-sized pulmonary vessels contained fresh or organized blood thrombi with an occasional one canalized, and as a consequence there were fresh and old infarcts. The cause of the thrombosis may have been either the abnormal and weakened myocardium or the tendency of the sickle-shaped red blood cells to agglutinate." Diggs and Ching state that "With the exception of sickled cells and the increased frequency of thrombi and infarcts the lung presents no unusual features. Pneumonia and tuberculosis are frequent."

Thrombotic phenomena are important episodes in the life history of patients with sickle-cell anemia. The organ most severely affected is the spleen. In a personal communication Diggs states that "Obliterative vascular changes and thrombi are surely a part of the pathological picture of sickle-cell anemia. We have observed organized and multiple thrombi in the lungs and in the spleen. The leg ulcers probably have thrombosis as part of their mechanism, and the patchy bone changes are those that would be associated with circulatory stasis. I have not noticed arteriolar sclerotic processes in the various organs except the spleen, but it is possible that it is generalized. The enlarged hearts these patients have and the maintenance of normal blood pressures in spite of very severe anemia and myocardial degenerative changes speak for peripheral resistance. I have thought that the shape of the cells was the explanation, and that the distorted, elongated forms favored stasis everywhere."

In Case 1 we have noted the same changes in the choroid plexus

as are found in the spleen in advanced cases. The pathology of the nervous system has not been adequately studied, but vascular phenomena have been observed clinically in the form of subarachnoid hemorrhage with cerebral softening in 1 child by Cook, and as hemiplegia associated with other cerebral disturbances in 2 children by Arena. It is possible that the abdominal crises and other pains may be due to vascular disturbances in the nervous system such as we noted in Case 1. Leivy and Schnabel have suggested the possibility of such an origin.

The puckered surface of the kidneys which is so frequently present is undoubtedly due to obliteration of the small arteries. The scars near the apices of the pyramids seem to be due to obliteration of the capillary bed between the collecting tubules. The engorgement of the capillaries of many organs attests the general vascular stasis.

The cause of the tendency to capillary engorgement and arterial thromboses is not definitely known. Diggs' theory that the distorted shape of the erythrocytes prevents their ready passage through the capillaries is probably a large factor in the general vascular stasis, aided by the apparent tendency of the cells to agglutinate. The studies of Scriver and Waugh are confirmatory of the probability that the degree of oxygen unsaturation is a large factor in the amount of sickling *in vivo*. Undoubtedly there is an increase in the degree of sickling *in vivo* from time to time depending upon the degree of capillary stasis and other factors. The amount of sickling seen in fresh blood smears probably does not represent the actual amount of sickling in the circulating blood, since the oxygen content of air tends to restore the shape of the erythrocytes. The study of the 2 cases here reported reveals the fact that the small arteries of practically all organs have been placed under severe prolonged strain, as evidenced by lengthening, tortuosity, hyalinization, hemorrhage into their walls and thrombosis. The site of the greatest stasis and obstruction is undoubtedly the capillary bed, through which the distorted erythrocytes have the greatest difficulty in passing. The burden placed upon the small arteries would explain well the vascular pathology.

Summary and Conclusions. 1. Two cases of sickle-cell anemia with hypertrophy and failure of the right side of the heart have been reported. In one, the heart failure was acute and manifested by orthopnea, great enlargement of the liver and dilatation of the heart. In the other, heart failure was not suspected clinically because of absence of orthopnea, but the liver became greatly swollen. Cyanosis was not present in either in life.

2. The cause of the right heart strain in the first case was thrombotic occlusions of the small and medium-sized arteries of the lungs, with organization and canalization of discrete thrombi which had formed from time to time. The heart failure was apparently precipitated by a final crop of fresh thromboses. The cause of the right heart failure in the second case was thickening of the walls

of the small and medium-sized arteries and the arterioles of the lungs with reduction in their lumens, but thromboses were not present in the tissue studied.

3. The absence of cyanosis is probably explained by the severe anemia, which prevents sufficient concentration of reduced hemoglobin to produce the picture of Ayerza's syndrome.

4. Right heart failure due to vascular changes in the lungs must be common in cases of sickle-cell anemia, since many of the patients have enlarged hearts, systolic murmurs and hepatomegaly.

5. Capillary stasis due to distortion and agglutination of erythrocytes is probably the essential factor in the changes described in the small arteries.

6. Changes in the nervous system are described in the first case, among which are the same lesions in the choroid plexus as are seen in the spleen in cases of advanced sickle-cell anemia.

7. The changes in the bone marrow differed from those previously reported in that they also were similar to those observed in the spleen.

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THE ELECTROCARDIOGRAM IN FEVER.

Changes in Induced Hyperpyrexia.

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The use of hyperpyrexia induced by physical means in the treatment of various ailments, has afforded us the opportunity of studying the changes in the electrocardiogram produced by fever uncompli-

cated by acute infection. Though this subject has considerable practical clinical importance as well as physiologic interest, it has been given little attention. Medical literature contains but few references and they deal almost entirely with animal experiments.[1,2,3,7]

We studied the changes occurring in 10 patients who could not be necessarily regarded as strictly normal[4] from the cardiac point of view, though the physical examination of the heart revealed no abnormalities and the electrocardiogram showed no significant changes. However, 1 case in which the *P–R* interval was prolonged was purposely included. All patients were afebrile.

The systemic temperature was elevated by means of diathermy and photothermy (Bierman[5,6]). The rectal temperature was raised to between 104 to 106.5° F. for a period varying from 3 to 5 hours. The electrocardiograms were taken before the establishment of the fever, at hourly intervals during its maintenance and shortly thereafter. An average of about 10 electrocardiograms were made during each fever session. During the recording, the diathermy current was discontinued and the patient was disturbed as little as possible. In several cases a small dose of a barbital compound had been given.

Rate Changes. With the inauguration of fever, the heart rate increased rapidly. In a previous series[9] of 500 cases it averaged 8.5 beats per minute for each degree Fahrenheit temperature elevation.

Bazett[7] observed in animals, that on the ascent of the fever, at the same temperature, the pulse was usually more rapid than when the fever was on its way down. Our findings were in accord with this. The maximum rate to which the pulse rose was usually between 146 and 162.

Electrocardiographic Changes. *P* wave. The amplitude changes were slight and not always in the same direction. In Lead I, the *P* wave became taller in 5 cases and smaller in 5, the greatest variations were an increase of 1 mm. and a decrease of .4 mm.

In Lead II, the *P* wave amplitude was increased in 3, diminished in 3 and both increased and diminished in 3 cases; in 1 case because of merging with the *T* wave, the *P* wave could not be accurately measured. The maximum variations for Lead II were an increase of 1 mm. and a decrease of .6 mm.

In Lead III, the *P* wave was more often increased in size. There were increases in 7 cases. In 1, the amplitude was diminished and in 2 it was both increased and diminished. Here the maximum change was from −1.4 to +.8, and increase of 2.2 mm.

The width of the *P* wave showed less variation. In most cases, slight changes took place, usually of about .01 to .02 second. In Leads I and II, the duration increased and diminished in an equal number, while in Lead III more were increased (6 to 3). The greatest variation was .04 second, an increase from .04 to .08 second and also a decrease from .07 to .03 second.

The *P–R* interval was diminished in all leads in all cases with one minor exception. It tended to parallel the temperature change. The greatest

reduction was .07 second, from .19 to .12 second. In 1 patient in whom the *P–R* interval was abnormal, .22 second, this interval was reduced to within the normal range during the fever.

Q–R–S. The amplitude of the *Q* wave in Lead I was unchanged in most cases. In 1 it was slightly increased (.7 mm.) and in 2 slightly diminished (.3 mm. and .9 mm.). In Lead II, it was unchanged in 5 cases, slightly increased in size in 3 and showed both increases and decreases in 2 cases. In Lead III, *Q* became deeper in 7 cases in 1 of which (B. M.) it increased sufficiently to fulfill the criteria for "prominent or significant Q_3." Its size was diminished in 1 case and unchanged in 2.

The *R* wave tended to become smaller with the increase in temperature of the patient.

In Lead I, the R amplitude was reduced in 5 cases, in 3 of which it was reduced to the normal borderline of 5 mm. or below. The greatest reduction was one of 6.5 mm., from 17 to 10.5 mm. In only 1 case was it increased.

In Lead II, *R* was decreased in size in 7 cases, in 2 of which it was reduced to 5 mm. or less; the maximum change was 7 mm. (10. to 3.). There was also an increase in 1 case and both increases and decreases in 2.

In Lead III, *R* was reduced in 5, 2 to below the normal borderline of 5 mm. In 2 cases, there were increases, both from below 5 mm. to above. In the remaining 3 cases it was both increased and decreased in each. These effects were not due to changes in the electrical axis which varied little. No slurring was produced.

The *S* wave showed a general tendency to be slightly increased in amplitude in Leads I and III. It was equally slightly increased and decreased in size in Lead II. The maximum variations were 2 to 3 mm. in Leads I and II, and 4.5 mm. in Lead III.

The general tendency for the *Q–R–S* interval was to become diminished as the body temperature rose. The maximum change was .04 second from a duration of .08 second to one of .04 second.

In the few remaining instances, there was either a slight increase in duration or no change at all.

R–T Phase. The *RT* level was depressed by the fever in Leads I and II in almost every case. In no instance was it elevated.

In Lead III, however, it was elevated in 5 cases, depressed in 2 and showed no deviation in 3.

The maximum variation was .6 mm., the usual .3 mm. The *RT* duration was decreased in all cases in Lead I. In Leads II and III it was diminished in 5 each—increased in 3 each, and both increased and decreased in 1 each.

T Wave. The *T* wave amplitude in Lead I had the same incidence of increases as decreases. In Lead II, it was slightly more often increased and in Lead III, much more often increased. The maximum increase was 4.5 mm.; that in Lead III. The maximum reduction was 3 mm., also in Lead III.

In 3 instances, in Leads I and II, *T* was reduced from a normal to an undersized wave, 1 mm. or less. In 2 instances, it was enlarged from a borderline size to one well above.

LEGEND FOR TABLES—LEADS I, II AND III.

The galvanometer is standardized to give an excursion of 1 cm. for 1 millivolt. All amplitude and level displacement measurements are in millimeters. All wave duration and interval measurements are in seconds. The first row for each patient, is the control reading taken before the beginning of temperature elevation. The second row records the maximum change during the temperature elevation; if both an increase and a decrease were present—both are recorded. b = biphasic; M = merged with *T* or *P* wave; * received morphin sulphate gr. ¼. The skin resistance was always between 1000 and 2000 ohms.

LEAD I.

	Age.	Highest temp., °F.	Hrs. of 104 or over.	Rate per minute.	P amplitude.	P duration.	P-R	Q.	R.	S.	Q-R-S interval.	RT level displacement.	RT duration.	T amplitude.	T duration.	TQ interval.
H. L.: Gonococcal arthritis	38	106.1^{R}	5.5	72 120	.8 1.	.10 .07	.16 .11	.3 0.	7. 3.5	0. .3	.06 .04	0. 0.	.14 .13	1.3 1.	.15 .12	.48 .18
B. M.: Gonococcal arthritis	36	105.8^{M}	3.5	94 133	1.5 2.5	.07 .08	.16 .12	0. 0.	11. 19.	2.5 .5	.07 .08	0. −.5	.08 .04	2. 4.	.14 .18 (.12)	.36 .16
E. H.: Multiple sclerosis	44	104.	?	92 120	1. 1.2	.06 .08	.12 .11	0. 0.	11. 5.	0. .8	.07 .06	0. −.5	.20 .10	−.8 −.2 −.3	.07 .09	.32 .24
M. L.: Gonococcal arthritis	20	106.1^{R}	5	67 146	.7 .3	.08 .08	.16 .14	0. 0.	7.5 4.	1.2 3.	.07 .05	0. 0.	.14 .08	2. 1.2	.12 .16	.63 .16
M. J.: Non-specific infectious arthritis	42	106.8	5.	73 188	.8 1.4	.09 .07 (.10)	.19 .12	.8 .6 (1)	11. 5.5	2. .2	.10 .07	.4 −.2	.10 .04	3. 1.4	.16 .12	.44 .10
H. H.: Non-specific infectious arthritis	20	105.9^{M} 106.1^{R}	5. ...	104 *122*	.6 *1.4 (.5)*	.08 *.10*	.14 *.13*	0. 0.	7. 5. (5.8)	4.5 6.5	.08 .08	0. 0.	.07 .03	2.2 2.8, 2.0	.14 .12	.28 .24
E. G.: Gonococcal arthritis	29	105.5^{R}	3.5	86 130	.8 .4	.08 .07	.13 .12	0. 0.	5. 6.5 (4.2)	0. 1.5	.08 .05	−.2 −.4	.16 .08	1.5 1. (1.6)	.16 .14	.30 .16
*E. H.: Gonococcal salpingitis	25	105.7^{M}	4.	107 143	.8 .5	.08 .06	.13 .08	1.7 .8	17. 10.5	2. 0.	.09 .06	0. −.4	.07 .10	2. 1.	.15 .18 (.22)	.24 .12
*J. G.: Asthma	47	106.4	3.	111 146	.5 .2 (.7)	.08 .04	.14 .12	0. .7	5.5 6.5 (4.2)	0. 2.	.06 .07	0. −.4	.10 .07	1. 3.3	.14 .12	.24 .14
A. R.: Gonococcal arthritis	34	106.4	3.	104 162	.8 .M	.08 .M	.22 .20M	0. 0.	6. 8.5 (4.5)	0. 0.	.065 .045	.2 −.2	.08 .06 (.11)	1.2 2. (.6)	.14 M	.29 .2 M

LEAD II.

	Age.	Highest temp., ° F.	Hrs. of 104 or over.	Rate per minute.	P amplitude.	P duration.	P-R.	Q.	R.	S.	Q-R-S interval.	RT level displacement.	RT duration.	T amplitude.	T duration.	TQ interval.
H. L.: Gonococcal arthritis	38	106.1 R	5 5	76 109	1 6 1.	1 .08	.15 12	.4 0 (.7)	10 7 (12)	0. 0.	.08 06	3 .0	14 06	2 3 5	14 22	.40 .18
B. M.: Gonococcal arthritis	36	105 8 M	3.5	92 133	2 3.	.08 .09	16 12	0 .0	8.5 17.	1 25 0.	08 07	.0 — .25	08 01	2 — ¼ + ½ b	.15 26	.34 .12
E. H.: Multiple sclerosis	44	104.	?	97 116	1 4 .9	.09 08	12 .10	0 .0	10. 3.	0. 7	.08 .05	— .3 — .8	12 10	— 1. — 4	.11 .08	.28 22
M. L.: Gonococcal arthritis	20	106.1 R	5.	67 146	.8 1 5 (.6)	.08 .08	16 .16	0 .5	11 7 5	0. .3	06 04	.2 0	16 07	2.1 3.	16 20	.60 .15
M. J.: Non-specific infectious arthritis	42	106.8	5.	72 162	7 1.8 (3)	.08 .10 (.06)	20 .18	0 .5	4 2 2 4	2 2 7	.08 .07	.4 — .2	.09 .05	2.7 1 4	.16 .11	.48 .16
H. H.: Non-specific infectious arthritis	20	105.9 M	5.	81 120	1. 1.4	.07 .10	.14 .13	.0 .0	5 5 6. (4.5)	3 5 (2 5)	.08 08	.0 .0	06 05	3. 2.	15 .14 (16)	.24 .22
E. G.: Gonococcal arthritis	20	106.1 R	5.	84 130	.2 1 2	.08 .08	.13 .16	.0 .0	12. 9.	.8 0.	.08 05	— 3 .0	.10 12	8 1 9	16 .14 (20)	36 19
*E. H.: Gonococcal salpingitis	29	105.5 R	3.5	102 150	1.2 .6	.08 .06	.15 .12	.3 .0	15.5 8.	3. .7	.07 .05	.0 — .4	.10 .09 (1 2)	(— 4 + 2 b) 2.4 0.	.14 .18 (.12)	.28 .13
*J. G.: Asthma	25	105.7 M	4.	113 146	2.1 1 7 (2 6)	.08 .08	.16 .15	.0 7	7. 3.5	0. 3.	.08 .06	.0 — .5	05 .11	2.4 6.	.20 .12	.20 .14
A. R. Gonococcal arthritis	47	106.4	3.	104 158	1 6 M	.09 M	.23 20M	0 .0	13. 7.	0 0.	.08 .045	— .2 — .4	.08 .11	1.4 2 2	.16 .12M	.26 .21M
	34	106.4	3.													

LEAD III.

	Age.	Highest temp., ° F.	Hrs. of 104 or over.	Rate per minute.	P amplitude.	P duration.	P-R.	Q.	R.	S.	Q-R-S interval.	RT level displacement.	RT duration.	T amplitude.	T duration.	TQ interval.
H. L.: Gonococcal arthritis	38	106.1	5.5	81 111	.7 1.2 (.6)	.07 .09	.15 .13	0. 0.	3. 5.5	0. 0.	.08 .09	.3 .0	.16 .04	.5 2.5 (−.3 +.8 b)	.10 .22	.40 .13
B. M.: Gonococcal arthritis	36	105.8	3.5	94 133	.5 2.	.07 .08	.16 .12	1. −4.	−3 5 −8.	1. 5.	.09 .08	.0 .25	.10 .04	−1. −4.	.08 .16	.36 .18
E. H.: Multiple sclerosis	44	104	?	97 120	.7 .5 (+.3 −.6 b)	.07 .06	.12 .10	0. 1.	2. −3.	−7. −2.5	.07 .06 (.08)	.0 −.2	.18 .10	−.5 4.	.08 .06 (.10)	.26 .20
M. L.: Gonococcal arthritis	20	106.1	5.	71 143	.3 .7	.04 .08	.16 .15	3. 1.4	5. 7.	0. 0.	.055 .05 (.06)	.0 .0	.18 .07	.8 1.6 (−.8)	.14 .10 (.20)	.68 .15
M. J.: Non-specific infectious arthritis	42	106.8	5.	73 167	−1. 1.	.07 .10	.18 .12	0. .7	1.6 −3.5	−6. 1.	.08 .06	.0 .0	.18 .0	−.7 1.	.10 .16 (.08)	.46 .16
H. H.: Non-specific infectious arthritis	20	105.9 M 106.1 R	5. ...	102 125	+.3 −.5 b .6	.08 .07	.14 .13 (.16)	2.2 3.5	4.5 7.5 (2.)	0. 0.	.07 .07	.0 .0	.07 .12	.6 .8 (.3)	.12 .08 (.16)	.32 .21
E. G.: Gonococcal arthritis	29	105.5	3.5	82 133	−1.4 .8	.08 .06	.16 .12	0. .6	9. 5.	0. 0.	.07 .06	.0 .3	.16 .08	−.7 .7	.12 .08 (.16)	.37 .14
*E. H. Gonococcal salpingitis	25	105.7	4.	102 146	.8 .4 (1.)	.07 .08	.12 .10	0. .6	1.4 −.2	2. 4. (−.3)	.08 .065	.0 −.3	.10 .08 (.12)	−.3 −1.2 (+.4)	.10 .08 (.16)	.30 .11
*J. G.: Asthma	47	106.4	3.	111 146	1.6 2.2 (1.1)	.08 .09	.16 .14	0. 2.	2. 2.6 (−1.4)	0. 1.	.07 .08 (.05)	.0 .2	Flat .14 (.09)	.5 2.	Flat 16. (10)	Flat .16
A. R.: Gonococcal arthritis	34	106.4	3.	100 158	.8 2.M	.10 M	.23 .21M	0. 0.	7. 1.5	0. 0.	.08 .04	.0 .0	.04 .16	−.4 .8	.12 .10M	.36 .22M

In 1 instance a 2 mm. T wave was flattened to the isoelectric level and in another a 2 mm. erect T wave was made biphasic.

In Lead III, in 3 instances an inverted T wave became erect.

Both increases and decreases occurred in each of 3 cases in Lead I, 2 cases in Lead II, and 4 in Lead III.

The duration of the T wave was only slightly more often diminished than increased (10 to 8). In Leads I, II and III, there were decreases in 5, 4 and 1 case respectively, and increases in 3, 3 and 2 cases. In the remainder, both increases and decreases were present in each case.

The T–Q periods from the end of the T wave to the beginning of the Q–R–S complex, the period of diastole, naturally diminished with the increase in rate. The relative change here, however, was greater than the relative change of the whole cycle length. The greatest diastolic reduction was from .68 to .15 second, over 78%, whereas the cycle length (R–R) was reduced only 50%, from .84 to .42 second for the same cycle.

From the above analysis and from references to the tables it is readily seen that fever, particularly the higher fevers, occasionally affected the electrocardiogram significantly. Some normal wave amplitudes and intervals, have become abnormal under its influence. Several abnormal values too were so altered as to come within the normal range. Expecially striking was this for the R and T wave amplitudes, the P–R interval and in 1 case the Q_3 depth. The appended table indicates in some detail the changes that occurred. Because of the small number of cases it is incomplete, but at present does give some idea of changes that may be attributed to fever.

Many of the electrocardiographic changes are probably due to the increase in rate. We have seen most of these P, Q–R–S and T wave changes produced by simple sinus tachycardia caused by exercise in a normal afebrile adult. However, we do not believe that the rate increase explains all. The group of chemical and physiologic changes which take place in fever, undoubtedly contribute to and modify the electrocardiographic effects of increased rate. These are especially the alterations in blood and tissue pH, carbon dioxid and lactic acid content,[7,8,9] etc., and in addition the changes in metabolism, blood pressure, blood flow and cardiac output.[1,7,8,9,10]

The electrocardiographic variations pretty much paralleled the temperature and rate changes. Starting with the beginning of the fever, they gradually reached their maximum at about the height of the temperature and receded with the temperature, frequently with some lag.

In most cases, there was a return of the electrocardiogram to the pretreatment appearance either immediately upon the cessation of the fever or shortly after. Alterations of interval were restored more promptly than the alterations of amplitude. No change was permanent. From these electrocardiographic changes, it cannot be inferred that any cardiac damage had been produced by the hyperpyrexia.

Summary and Conclusion. Observations were made on changes in electrocardiograms produced by fever of between 104 to 106.5° F., of 3 to 5 hours' duration, induced by physical means.

Changes in rate were described.

The alterations of electrocardiographic waves were not uniform. P and T waves were almost as frequently increased in size, as decreased. The R wave, however, most often became smaller and the P–R and Q–R–S intervals in most instances were shortened.

The RT level was usually depressed, never elevated.

Of special significance was the transformation of several normal

amplitudes or intervals to abnormal ones, as well as the reverse. This involved particularly the R and T amplitudes. Worthy of mention is the development of a prominent Q_3 in one instance.

The mechanism of electrocardiographic changes is probably through reflexes, tachycardia, local cardiac and general chemical and physiologic alterations.

None of the electrocardiographic changes were permanent. No inference could be made that the fever produced any harmful effects upon the heart.

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STRENGTH DURATION CURVES OF THE OVEREXCITABLE AND UNDEREXCITABLE NERVE MUSCLE APPARATUS AND SOME CONSEQUENCES BEARING ON THE CLINICAL APPLICATION OF CHRONAXIMETRY.*†

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Lapicque has proven experimentally that the strength duration curve of different tissues—except for very short times—was approximately an hyperbola. This conception was completely corroborated by Sakamoto (1933) stimulating single motor nerve fibers.

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Corresponding to the definition of the hyperbola, two determinations —representing rheobase and chronaxie—should, therefore, determine the actual strength duration curve and simultaneously the irritability of the examined tissue. It is the teaching of the French school that even one of them, the chronaxie, should determine exactly enough—at least for clinical purposes—the irritability of a given tissue. The simplicity of this one figure as a result of the electrical stimulation is the more appealing, as Lapicque had assumed a fixed relation of 4 to 1 between chronaxie and his time constant θ.

Lapicque's experience, however, was confined mostly to the normal nerve muscle apparatus. Whether chronaxie alone is a suitable index of irritability under pathologic conditions also, is still open to discussion.

The practical application of chronaxie in clinical medicine depends, therefore, upon the following questions:

1. *a.* Whether the strength duration curve of the overexcitable and underexcitable nerve muscle apparatus is an hyperbola as well as that of the normal one; and if that is true:

b. In what way the hyperbolæ of overexcitable and underexcitable individuals differ from the normal and from another.

2. What symbol can best characterize the shape of these curves.

Eight hundred and twenty-five lead workers subjected to different degrees of exposure were chronaximetrically examined at the superior optimal point of the extensor digitorum communis percutaneously by means of a condensor apparatus with about 11,000 ohms resistance and with help of a constant source of current read off to 1 v.

§ 1. The *strength duration curve of normal, of definite overexcitable and definite underexcitable* individuals was established on about 6 points. Figure 1 gives a number of such curves; Figure 2 shows representatives of each of these 3 categories in a larger scale.

a. Plotting quantity against time, it was found that the Weiss-Hoorweg line in all three curves of Figure 2 was a straight line—except for very short times. This observation emphasizes the probability that the *curves are in fact hyperbolæ.*

To verify the result, according to Hoorweg's formulæ of the strength duration curve, the constants *a* and *b* were calculated from two determinations of voltage and time (1 and 3 of the following example). The resulting figures were put into a third value next to or between the two first (middle value of the example) and the voltage was calculated. The calculated voltage and the observed voltage differed from 3 to 7.5%.

Normal.		*Overexcitable.*		*Underexcitable.*	
200V—0.16σ		135V—0.8σ		200V—0.16σ	
190V—0.48σ	205V = 7.9%	110V—2σ	116.5V = 5.5%	175V—1.36σ	169.6V = 3%
160V—1.4σ		100V—7σ		150V—2σ	
a = 72		a = 47		a = 8.6	
b = 155		b = 93		b = 145.7	

b. Comparing the shape of the curves in Figures 1 and 2, we observe that they are entirely different in their curvature. The curvature is smallest in overexcitability and greatest in under-

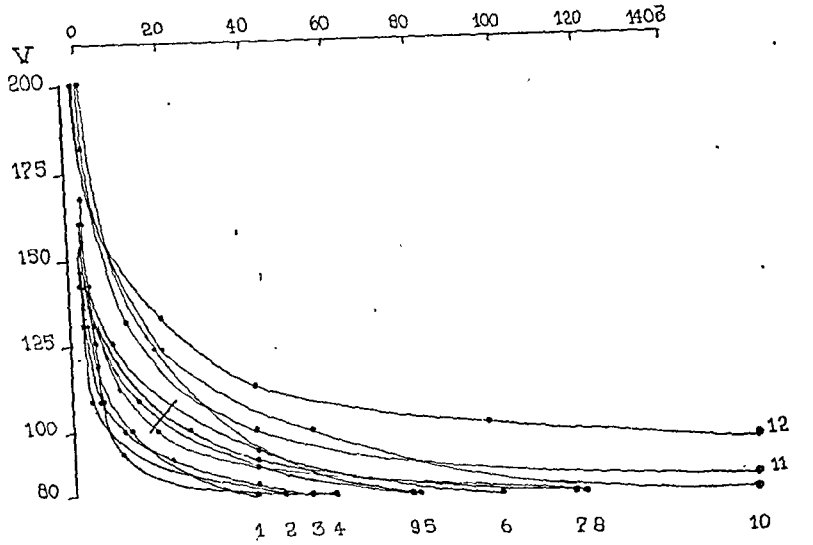


FIG. 1.—A number of strength-duration curves from overexcitable, normal and underexcitable individuals. The line uniting the vertex points is drawn only in the range of the normal.

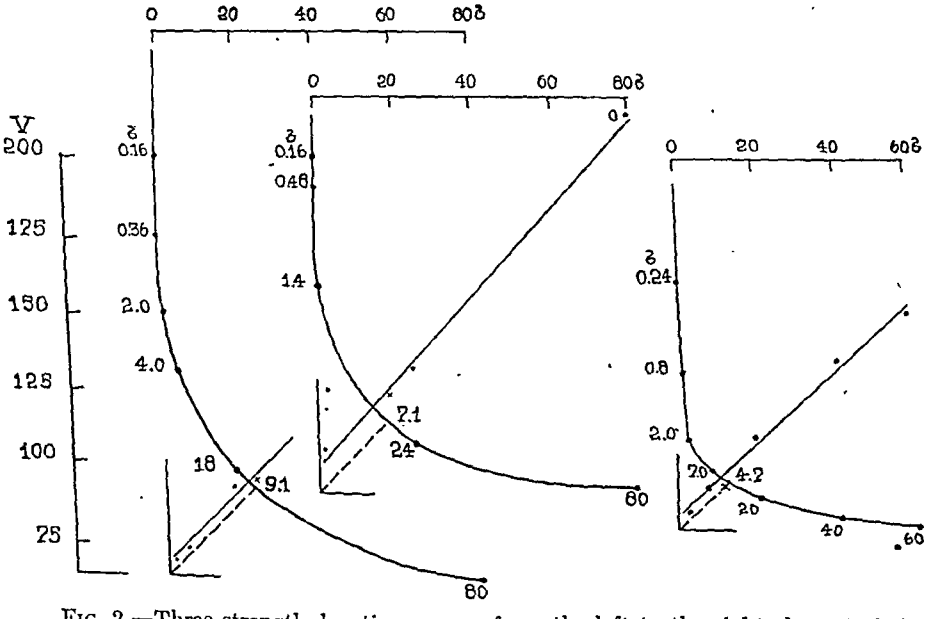


FIG. 2.—Three strength-duration curves, from the left to the right characteristic of an underexcitable, a normal and an overexcitable subject. The right angles signify the position of the respective zero point of the coördinate axes. The dotted line bisecting this angle intersects the curve in its vertex. The vertex characterizes the shape of the curve (hyperbola). Its index is equal to the square root of the product of rheobase and chronaxie (vc.). The full straight line connecting the various points is the Weiss-Hoorweg line.

excitability, and lies between the two values in normal individuals. This means that *the curvature formed by the two branches of the strength duration curve characterizes the degree of irritability.*

§ 2. If this is true, the best symbol of the strength duration curve would be an index giving the clearest reading of the curvature. The position of the *vertex of the hyperbola, i. e.*, the vertex coördinates, would best serve this purpose.

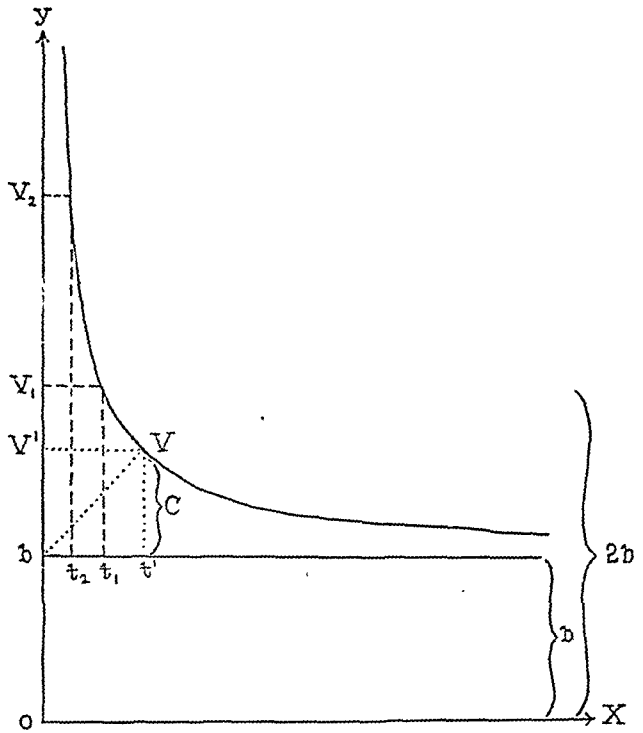


FIG. 3.—Diagram of a hyperbola within a rectangular coördinate system: x = time axis, y = volt axis, b = rheobase. The corresponding chronaxie determined with 2b (V_1 Volt) is equal to t_1. t_2 designates the time with a voltage somewhat higher than the doubled rheobase (V_2). V = vertex of the hyperbola, V' and t' the corresponding voltage and time. VV' = Vt' = C.

The straight line bisecting the right angle of the coördinate system, formed by the vertical volt axis and the horizontal time axis at the level of the rheobase *b*, intersects the hyperbola in its vertex (Fig. 3). The position of the vertex, according to the definition of the hyperbola, can be calculated as the square root of the product of rheobase by chronaxie, *i. e.*, of half of the quantity. The length of this vertex coördinate was measured in determined and outlined strength duration curves and compared with the results of hundreds of calculations in normal and pathologic individuals as to our test muscle (extensor digit. comm.). This muscle has a normal rheobase of 90 to 45 volts with a corresponding chronaxie of from 0.4 to 0.8σ. The statistical norm of the vertex co-

ordinate under these conditions was between 6 and 9 units of measurement. Figures below 6 indicate a more rectangular curve—as characteristic of overexcitability—while figures above 9 give a more obtuse angle—as characteristic of underexcitability.

The given formula (I) $C = \sqrt{rh \times chr}$, in which C designates the vertex coördinate, rh the rheobase and chr the chronaxie, makes it obvious that the rheobase cannot be a negligible factor, as even with identical chronaxie the shape of the hyperbola varies widely subject to the rheobase. This is not so important in normal cases, as normally the rheobase is relatively constant with the same resistance and the same muscle. But with a change of temperature and blood flow or under the effect of different mineral salts and drugs the rheobase may be indispensable for final decision, especially when the chronaxie is verging upon overexcitability or underexcitability.

In *physiological experiments* it is certainly the most suitable procedure to plot quantity against time, to control the straightness of the Weiss-Hoorweg line and to compare it in a diagram with an average standard line. For *routine neurological examinations,* however, this method is somewhat complicated. We found a simpler method in deriving the vertex coördinate of the correspondent hyperbola directly from the determinations.

According to Figure 3: $C = \sqrt{V_1t_1 - bt_1} = \sqrt{V_2t_2 - bt_2}$. If t_1 is the chronaxie, V_1 its double rheobase, *i. e.,* 2b:

(I) $C = \sqrt{(2b - b)t_1} = \sqrt{bt_1} = \sqrt{\text{rheobase} \times \text{chronaxie}}$. (I) First determination.

(II) $C = \sqrt{(V_2 - b)t_2}$ Valid for a second pair of determinations, *e. g.,* 20V above the doubled rheobase.

(III) $C = \sqrt{\frac{(V_2 - V_1)t_2t_1}{t_1 - t_2}}$ Determines C in a somewhat different way.

Substituting the observed values into the formulæ I to III the values of C usually vary in some degree. The mean value of the three readings—to be called *vertex characteristic,* vc.—seems to be a good symbol of the hyperbola representing the strength-duration curve.

We preferred this form of presentation, going down to the coördinate C for its greater visuality and for the direct comparability of the obtained results with those measured in determined and outlined strength-duration curves. The square root of the product of voltage and time is so easily read off from a table that we applied the square root not only in these theoretical deductions but also in our practical examinations (Lane and Lewy, 1935). However, there is no objection in resigning to draw the root and in using the constant C^2 instead of C. Under these conditions the norm in our case is from 36 to 81 instead of from 6 to 9.

§ 3. In order to prove this statement it will be shown that:

(*a*) The vertex of the strength-duration curve, calculated according to the three given formulæ from two pairs of measurements coincides in first approximation with the vertex of the observed curve, and

(*b*) The ordinate of the hyperbola constructed at the "calculated" vertex (as above) coincides approximately with a third "observed" point of the curve which is not used in the calculation.

a. We designate the vertex characteristic vc. as "calculated" when it represents the mean of the 3 results determined with help of formula I to III. We designate it as "observed" when it represents the measured vertex coördinate of the determined strength duration curve outlined on millimeter or inch paper.

			Calculated vc.	Observed.
1. 100V—0.28σ . . .	I. 5.2	III. 3.8		
175 —0.56σ . . .	II. 6.4	vc. 5.1	5.1	5.0
2. 65V—0.32σ . . .	I. 4.5	III. 3.6		
150 —0.16σ . . .	II. 3.7	vc. 3.9	3.9	3.5
3. 70V—0.2σ . . .	I. 3.8	III. 2.4		
120 —0.6σ . . .	II. 5.4	vc. 3.9	3.9	4.1
4. 80V—0.24σ . . .	I. 4.4	III. 3.2		
130 —0.8σ . . .	II. 6.3	vc. 4.6	4.6	4.7
5. 95V—0.48σ . . .	I. 6.7	III. 4.7		
160 —1.4σ . . .	II. 9.5	vc. 7.0	7.0	7.5
6. 80V—0.68σ . . .	I. 7.4	III. 6.6		
200 —0.36σ . . .	II. 6.6	vc. 6.9	6.9	7.0
7. 90V—0.8σ . . .	I. 8 5	III. 7.5		
200 —0.7σ . . .	II. 8.8	vc. 8.3	8.3	8.4
8. 65V—0.6σ . . .	I. 6.2	III. 7.7		
150 —0.5σ . . .	II. 6.5	vc. 6.8	6.8	6.2
9. 65V—4.0σ . . .	. . .	III. 8.9	8.9	9.8
10. 65V—4.0σ . . .	I. 16.0	III. 6.3		
170 —0.8σ . . .	II. 8.6	vc. 10.3	10.3	10.7
11. 80V—2.8σ . . .	I. 14.4	III. 6.7		
200 —0.8σ . . .	II. 9.8	vc. 10.3	10.3	9.7
12. 70V—4.0σ . . .	I. 16 8	III. 10.3		
180 —0 8σ . . .	II. 8.5	vc. 11 9	11.9	12.2

Although the decimals of the observed values are merely estimated and consequently inaccurate, *the coincidence of calculated and observed vertex coördinates is very satisfactory.*

b. For reasons which will be discussed in § 6 anode strength duration curves were observed and were constructed as hyperbolæ at the calculated vertex, according to the 3 given formulæ. Furthermore, in all of these curves the time was determined at the level of the doubled cathode rheobase. This third "observed"

time value, not used in the calculation, was compared with the time of the constructed curve at the same level.

Calculated time.	Observed time.
2.2σ	1.4σ
0.8σ	1.2σ
6.8σ	6.8σ
3.5σ	4.0σ

As the first column represents points of a mathematical curve, and the second represents values of percutaneous measurement, and therefore relatively inexact, the correspondence seems quite satisfactory.

We may accordingly conclude that:

1. *Strength duration curves of the overexcitable and underexcitable nerve muscle apparatus are hyperbolæ, differing in the degree of their curvature.*

2. *By means of two independent measurements of the excitation time—one of which may be the chronaxie—and by three simple calculations we can determine the "vertex characteristic" (vc.). This symbol defines with sufficient exactitude the shape of the hyperbola upon which the chronaxie is situated.*

From these theoretical deductions follow practical consequences which seem to be of importance in the application of chronaximetry to clinical medicine.

§ 4. Every experienced examiner knows how difficult it often is to determine even in normal individuals in percutaneous examination the optimal point. Under pathologic conditions it may remain still more questionable whether the point stimulated at the skin is really the most irritable. In consequence of this experience even so skillful an investigator as Bourguignon emphatically reiterates that one should not rely on the result of one single chronaximetric examination unless it be verified by a second and third investigation.

These experiences made it desirable to evolve a *routine method* permitting it to be established *whether or not the stimulated point is really the optimal one.* We designate as the "optimal" point the most irritable one, or more exactly, such a point on the skin by stimulation of which the virtual cathode within the nerve gets its greatest density. If this point is stimulated with a higher voltage, the time required for excitation decreases *pari passu,* while the product of the two, after subtraction of the rheobase, remains equal. This is not so if any other point at the skin is stimulated. It has been our experience that if such a non-optimal point is stimulated with a higher voltage, the corresponding time does not seem to decrease in reciprocal ratio; consequently the product of voltage by time is not unvariably the same. In other words, on

stimulating the optimal point on the skin, the strength duration curve is a hyperbola; while on stimulating any other point this does not seem to be the case.

This result of a great number of investigations in pathologic conditions coincides with the findings of Büssow in normal individuals. Büssow showed that stimulating a skin point in the distance of $\frac{1}{2}$ inch from the real optimal point the strength duration curve of a normal muscle may become discontinuous.

As it is impossible in routine medical examinations to determine each time the whole strength duration curve, it is certainly advisable to determine, instead of one, at least two points of the curve, and to prove that they are part of the same hyperbola.

§ 5. However, *in the first stages of a nerve lesion*—though depending on its character—and in the last stages of regeneration, it is usually *impossible to obtain a satisfactory approximation* of the three values of vc. This implies that not all points of this strength duration curve were situated upon one and the same hyperbola. In fact, Adrian has shown on the degenerated facial nerve that *such curves, as a rule, are discontinuous.*

This fact, of course, is not rendered visible if the chronaxie alone is measured, nor is it apparent in the vertex characteristic calculated from chronaxie and rheobase only. But it may be suspected, if one cannot get a close approximation of the three vertex values, especially when the values of formula III spread over a wide range.

(I) V_1 (rheobase) 80V, t_1 (chronaxie) 3.6σ vc. 16.9
(II) V_2 200V, t_2 1.6σ vc. 13.8
(III) vc. 10.9

Under these conditions we are able to calculate the rheobase of the assumed second hyperbola and its vertex from V_1, t_1 and t_2 by formula IV.

$$\text{(IV)}\quad b = \frac{V_2 t_2}{t_1 + t_2} = \frac{200 \times 1.6}{3.6 + 1.6} = 61.5\text{V}$$

Let us suppose, according to this calculation, that the two determined points are part of two hyperbolæ, the rheobases of which are 80 and 60 V respectively, then we can record it as in Figure 4. The full line in Figure 4 shows the discontinuous curve, as the combination of both the dotted and the lined hyperbola. Assuming the breaking point of the curve at 160 V was the rheobase of the superior (full) curve the chronaxie of this hyperbola was 0.88σ, *i. e.*, about normal. This corresponds to Adrian's curves. He found the chronaxie of the steep part of the curve during the process of degeneration practically unchanged, while the chronaxie of the flat curve increased gradually. Not until the degeneration was complete was a uniform smooth hyperbola again found, now with an obtuse curvature.

§ 6. Finally, we followed up the *anode excitation time* in connection with Pflüger's law. Some of the anode strength-duration curves were determined, others were calculated and constructed on the basis of their vertex characteristic. Figure 5 shows that in the majority of our cases the threshold for the cathode was lower than that for the anode. We did not observe in our cases a reversal of the galvanic excitability. The difference between the cathode and anode threshold was greater in pathologic than in normal muscles.

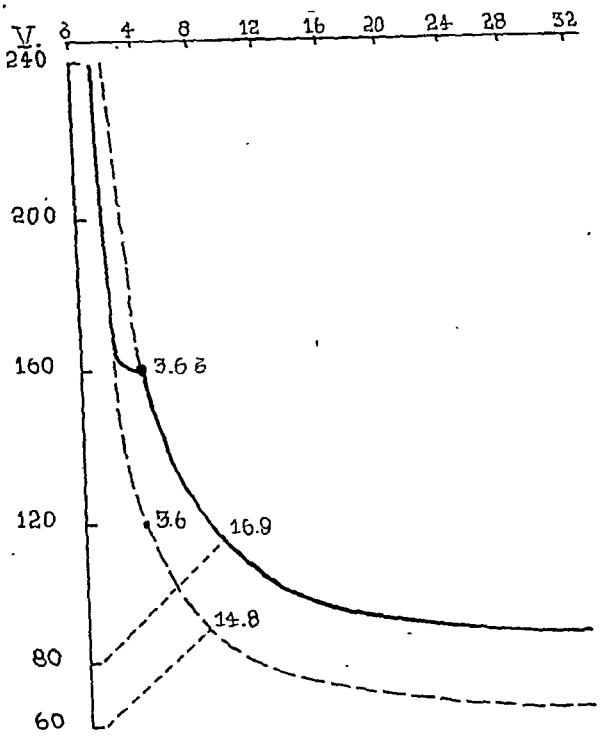


FIG. 4.—Diagram illustrating the constituents of a discontinuous strength-duration curve. It results in the combination of two (constructed) hyperbolæ. The chronaxie of the superior curve is normal with 0.8σ, that of the inferior is underexcitable with 3.6σ.

The most interesting fact, however, seemed to be *the crossing of the cathode and the anode curve upon the vertical axis as a first step towards the inversion of the excitation law.* This means that at the level of the doubled cathodic rheobase the anode excitation time became shorter than that of the cathode excitation time. In other words, *the excitation rule and its inversion applies* not only and not primarily to the galvanic threshold but *also and even earlier to the excitation time* (Fig. 5, curves 4*a* and 4*b*).

Discussion and Conclusions. In looking through the literature on clinical chronaximetry we see that almost constantly the rheobase values were omitted in the results, although they had to be determined to get the chronaxie values. Such a procedure may be per-

missible under certain conditions but not so as a rule. Local anesthetics, for instance, will, according to their concentration, increase the rheobase and decrease the chronaxie with the effect that their product, the minimal electrical quantity required for stimulation, remains about the same in cocain and novocain narcosis, but is considerably increased in pantocain and percain narcosis (Laubender and Raufenbarth). Exact consideration of the rheobase is also

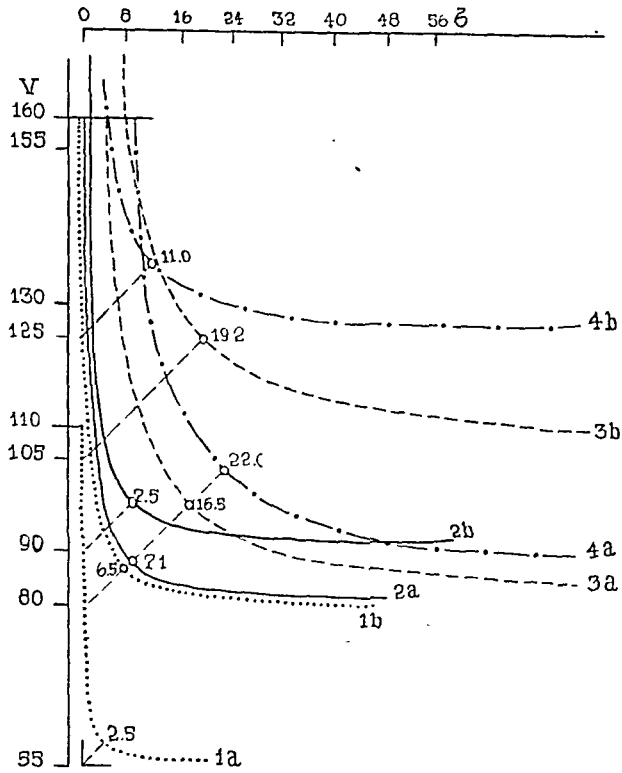


FIG. 5.—Four pairs of strength-duration curves. Each pair represents the cathode (*a*) and the anode curve (*b*) of one individual; 1*a* and *b* of an overexcitable, 2*a* and *b* of a normal, 3*a* and *b*, 4*a* and *b* of two underexcitable subjects. With the exception of 4*a* and *b* rheobase and chronaxie is shorter at the cathode than at the anode. With progressing underexcitability, however, the anode chronaxie becomes shorter than the cathodic one (4*a* and *b*), even before the anodic threshold grows smaller than the galvanic threshold (galvanic overexcitability). First stage of inversion of Pflüger's law.

required in order to understand the changes of nerve irritability under physiologic conditions such as during hyperventilation or anoxemia in great altitudes. *Neither rheobase alone nor chronaxie alone give the right impression of irritability.* The rheobase, however, gets its significance only through chronaxie. If that is so it is very important that *both parameters of irritability be included in the given result;* and that the rheobase should not be omitted. On the other hand, the simultaneous comparison of two rheobase and two chron-

axie values complicate the method for practical use. The length of one of the equal coördinates of the vertex of the hyperbola, representing the strength duration curve, is likewise given by one figure only. But since this one figure equals the square root of rheobase and chronaxie, it helps, in fact, to get rid of the rheobase. That is the reason this figure is superior to chronaxie alone. It, furthermore, conveys a clear idea of the shape of the hyperbola in representing a definite strength duration curve.

There are, no doubt, many cases in which a single chronaximetric examination and the statement of chronaxie alone give results sufficiently unequivocal to render any further test superflous. We class under this heading the majority of normal cases and all distinctly abnormal, more particularly underexcitable, subjects. Such clear cases, however, are found less frequently than may be supposed. Applying chronaximetry to persons not ill in the proper sense but exposed to noxious agents, as in industry, a greater part of the subjects examined was found to be on the borderline between normal and abnormal (Lane and Lewy, 1935). This is where the new index proved very helpful.

The same question has to be considered concerning the *optimal stimulation point* of a muscle upon the skin. This point is seemingly very easily found from one of the textbook diagrams. But in reality the situation of this point varies even in the normal from man to man. Under pathologic conditions the point may sometimes be hardly greater than a pinhead. The superior and inferior optimal point showing entirely different normal values, may be distant only $\frac{1}{4}$ inch from one another. Finally, no reliable chronaxie may be obtainable at the point of the lowest galvanic threshold. If, however, to overcome these difficulties greater capacities and lower voltage is applied, the skin is charged in increasing degree and the rheobase varies from one experiment to the next. To avoid this a much higher resistance (of ca. 100,000 ohms) in series to the skin would be required, with a corresponding higher voltage. This again is too dangerous in man and involves other difficulties (sparks, etc.). Accordingly, sufficient time must be allowed to elapse before the determination is repeated. But if the same point is stimulated several times in succession, especially with longer duration, the time values begin to flicker. Even with considerable experience in chronaximetric measuring, it may in pathologic cases take a quarter of an hour or longer to find the correct chronaxie of a single muscle point.

These observations lead to the setting up of the postulate that the correct position of the stimulation point should be objectively demonstrable. By determining besides rheobase and chronaxie a second time value with a strength of current about 20 V above the doubled rheobase, and by a simple multiplication, it seems to be possible to state with an accuracy sufficient for percutaneous clinical

examinations whether or not the optimal skin-muscle point is stimulated or whether the curve is discontinuous. In this case the rheobase of the second hyperbola can be easily extrapolated. Such a procedure proved to be more important as our examinations, corresponding to those of Adrian, showed that the discontinuous strength duration curve is neither a rare occurrence nor always the sign of an error in technique. The discontinuous curve rather represents a regular, though temporary stage during degeneration and regeneration.

Finally, our observations on Pflüger's law indicate a facilitation of the routine work in underexcitable cases. The direction of current has to be reversed at any rate during each examination, in order to counteract the skin polarization. What remains to be done in the quoted cases is to observe at this time whether the same condenser, the discharge of which produces the first twitch at the cathode is effective at the anode as well. If so we are faced with the first indication of a qualitative alteration of Pflüger's law.

Summary. Although it is generally accepted that the strength-duration curves of the normal nerve muscle apparatus are approximately hyperbolæ this has not yet been proven under pathologic conditions, *i. e.*, in overexcitability and underexcitability.

1. By means of chronaximetrical examinations of 825 lead workers subjected to different degrees of exposure it could be shown that the strength-duration curves of the overexcitable and underexcitable nerve-muscle apparatus equal approximately a hyperbola.

2. The hyperbolæ of normal, of overexcitable and underexcitable individuals differ in the degree of their curvature. The legs of the hyperbola of an overexcitable muscle form a more acute curvature, those of an underexcitable a more obtuse curvature. Normal curves lie between the two extremes.

3. The most suitable symbol of characterizing an actual strength-duration curve and indicating simultaneously its shape is the vertex of the hyperbola. The coördinate of the vertex—which may be called "vertex characteristic" (vc.)—equals the square root of the product of rheobase by chronaxie or in other words of half of the quantity. By this method one single and easily comparable figure is obtained. This single figure unmistakably characterizes the actual strength-duration curve.

4. Three simple formulæ are given to calculate the vertex characteristic by help of two independent pairs of measurements, carried out at one and the same muscle point. The approximate coincidence of the three values seemed to confirm that it was really the optimal point that was stimulated.

5. In the first stage of nerve degeneration and in the last stages of regeneration not all points of the strength duration are situated upon the same hyperbola. The curve becomes discontinuous, indicating that it consists of two distinct hyperbolæ. Under these con-

ditions the rheobase of the second hyperbola can be calculated by a simple formula from the two determinations.

6. The inversion of Pflüger's law applies to the excitation time as well. Even before the galvanic threshold with the anode sinks below the threshold with the cathode, the excitation time with the anode becomes shorter than that with the cathode.

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IS THE USE OF INSULIN INDICATED IN THE ELDERLY DIABETIC WITH CORONARY SCLEROSIS?

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Warning notes have appeared in the literature against the use of insulin in the diabetic who has manifestations of vascular degenerative disease because of the danger of precipitating vascular spasms or thromboses during hypoglycemic attacks.

Vascular crises are recognized to occur most commonly in arteries that have undergone sclerotic degeneration as a result of essential hypertension or progressive involution with aging. Reports in the literature[1,2,3] indicate that these sclerotic lesions are a more frequent phenomenon in the diabetic than the non-diabetic and in the poorly treated diabetic than in the well-controlled diabetic.

This paper is concerned with a critical analysis of the use of

insulin and an expression of opinion as to whether there is adequate justification for the feeling that insulin is contraindicated in the treatment of the elderly diabetic.

Before discussing this subject, it is well to review some of the physiologic and pharmacologic properties of insulin. In the pancreatectomized animal, insulin produces a disappearance of sugar from the blood with an attendant rise in the respiratory quotient, indicating that it is associated with the oxidation of glucose. That insulin also causes the deposition of glycogen in the liver and muscles has been demonstrated by the marked glycogenetic recovery which follows the administration of insulin in animals whose liver glycogen has been depleted by pancreatectomy.[4] Collens and Murlin[5] have suspected a third function of insulin, that of glycogenolysis. They have observed that the injection of insulin into the portal vein produces a transient hyperglycemia which could be explained only on the basis of its coming from liver glycogen. Dudley and Marrian[6] showed that excessive doses of insulin in rats are able to reduce liver glycogen. In view of the observation of Warburg, that the contraction of muscle tissue is associated with the anaërobic oxidation of its muscle glycogen, it would then appear that the function of insulin, in quantitatively regulating the deposition of muscle glycogen would have an extremely important clinical bearing upon the ability of muscle to contract. It is the belief of the authors that the clinical symptoms of muscle weakness and nocturnal claudication which exist as such outstanding symptoms in the diabetic with a severely broken sugar tolerance are the result of the depletion of glycogen from skeletal muscle. The rapid disappearance of these symptoms immediately after the administration of insulin with a liberal amount of carbohydrate helps to confirm our belief that improvement has been attended by the phenomenon of glycogen synthesis in muscle.

The authors who have warned against the use of insulin in the elderly diabetic have based their statements upon definitely observed toxic phenomena produced by administration of this hormone.[7–12] They report various types of disturbances in cardiac function associated with a state of insulin hypoglycemia, such as attacks of paroxysmal fibrillation, angina, and definite electrocardiographic changes, among which are notching of the P waves, prolongation of P–R interval, occasional slurring and prolongation of Q–R–S complex, changes in the deflection of S–T segment and alterations in the character of the T wave, such as flattening, prolongation and diphasic.

Some of these authors[2,7,12] have observed the beneficial effect that glucose has on the anginal attack during the hypoglycemic state. Smith and his co-workers[13] have even commented on the distinct beneficial effect of a high-carbohydrate diet in the treatment of cardiac failure in the non-diabetic. Intravenous injections of

50% glucose have been recommended in the treatment of coronary thrombosis,[14] since it furnishes the heart muscle with extra glucose and has a diuretic effect.

In a paper on poisons, Abel[15] presents an interesting concept of the relationship of poisons to therapeutic agents. To quote from his article: "The harmful effects of a large dose of a drug or poison do not fall off *pari passu* with the diminution in dose. On the contrary, with the diminishing dose there may occur a turn-about in the action of the drug with the appearance of a highly beneficial action, one indeed that is indispensable for the continuance and maintenance of health, as is the case when we pass from the toxic dose of a hormone to its therapeutic dose." Insulin is an excellent example of such a substance, indispensable to life and circulating in our blood below a toxic level, which, when increased in the circulation either by injection or due to hyperfunctioning pancreatic island tumors, results in profound degrees of intoxication violent enough to produce death.

Since insulin is able to deposit glycogen in tissues, we must think of it as a possible therapeutic agent in angina pectoris provided the toxic effect of vascular spasm and depletion of tissue glycogen is strictly avoided. Diabetics suffering from attacks of angina pectoris who showed electrocardiographic evidence of myocardial change as well as those in whom the tracings were normal were selected for this study. All types of cases, mild and severe diabetics, male and female, with and without evidence of organic heart disease, but all complaining of typical attacks of angina pectoris, were given a high-carbohydrate diet with sufficient insulin to relieve the diabetic picture both clinically and chemically. For purposes of brevity we shall present only a few isolated but typical case histories.

Case Abstracts. CASE 1.—Celia K., aged 60, was admitted with a history of typical diabetic symptoms of 3 months' duration and paroxysmal attacks of severe precordial pressure, dyspnea and palpitation for 1 year which had become aggravated since the development of her diabetes. Physical examination showed early bilateral cataracts, a dry and beefy tongue, auricular fibrillation, blood pressure 186/100, liver large and tender, congestive râles at the lung bases and ankle edema. She excreted 37.5 gm. of sugar in 24 hours and showed 1+ acetone. Her fasting blood sugar was 264 mg.%. She was put to bed, given a diet of C., 200, P., 60, F., 100 (salt-free), with 15 units of insulin, t. i. d., and 15 gm. of available glucose 2 hours p. c., t. i. d. Fluids were restricted to 1000 cc. She was given digitalis (1.5 gr., t. i. d.) and neptal (1.5 cc. intravenously) every other day. In 3 days her fibrillation stopped. Electrocardiogram (Fig. 1), taken at this time, showed evidence of myocardial damage. Two weeks later, she was discharged with her heart compensating and her anginal symptoms gone. Her blood sugar was then 184 mg.% and she showed traces of sugar in her urine. On 2 occasions in the past 18 months she experienced breaks in cardiac compensation precipitated by excessive physical exertion. During these episodes she again fibrillated, but her anginal symptoms were minimal. The interval periods have been entirely

free of anginal attacks. She has been maintained on the above diet and her insulin was reduced to 20 units per day.

Case 2.—George P., aged 64, machinist, 3 months before admission, started to complain of frequent attacks of precordial pain, grip-like in character, and dyspnea brought on by the slightest exertion. He had no diabetic symptoms. He was an obese individual with no positive physical findings except a blood pressure of 180/96. He excreted 2.5% sugar in a casual specimen and his fasting blood sugar was 211 mg.%. His electrocardiogram showed no evidence of myocardial damage (Fig. 2). He was given a diet containing 1200 calories and 258 gm. of available glucose with 35 units of insulin in 2 divided doses. He was protected with postcibal feedings. During the 8 months on this treatment his anginal syndrome has almost entirely disappeared. He does not volunteer any complaints, but on close questioning he states that he is able to elicit a mild precordial discomfort on very marked exertion of an order much out of proportion to that which he previously dared to engage in.

Case 3.—Isidore C., aged 67, was admitted with a history of diabetes of 1 month's known duration. His chief complaint was attacks of precordial pain, with pain also on the right side of his sternum, pressing in character and no radiations. These pains were elicited by walking half a block, and also occurred after meals. The pain was attended by dyspnea, would last 1 to 2 minutes and was relieved by rest. He had no diabetic symptoms. Physical findings disclosed an obese, plethoric, middle-aged man, with heart enlarged, second aortic sound accentuated and blood pressure 170/80. Teleoroentgenogram showed an enlarged hypertensive heart with widening of the aortic arch. Electrocardiogram (Fig. 3) showed evidence of myocardial damage. His urine contained traces of sugar and his blood sugar was 243 mg.%. He was given a diet containing C., 175, P., 51, F., 47, with 10 units of insulin once a day and 15 gm. of carbohydrate 2 hours after his insulin. In the 4 months since he has been on this treatment he has not experienced any anginal pains, either by walking a distance of 7 blocks or after meals.

Case 4.—Reuben M., aged 47, was admitted, April 15, 1932, complaining of attacks of precordial pain radiating to the left arm. He had been diabetic for 11 years. Physical examination disclosed no pathologic findings. Blood pressure, 128/90. Electrocardiogram showed left axis deviation. His urine was free of sugar and his blood sugar 210 mg.%. He was given a diet of C., 150, P., 75, F., 70. After his urine remained sugar-free for 8 months, his tolerance suddenly broke and was followed by an aggravation of his stenocardial syndrome. A reduction in his diet to C., 90, P., 60, F., 70. without insulin controlled his diabetes, but his anginal symptoms persisted. He was then placed on a high-carbohydrate diet, C., 220, P., 60. F., 75, with 10 units of insulin, t. i. d., which was followed by a

Legends for Figs. 1, 2, 3, 4 and 5.

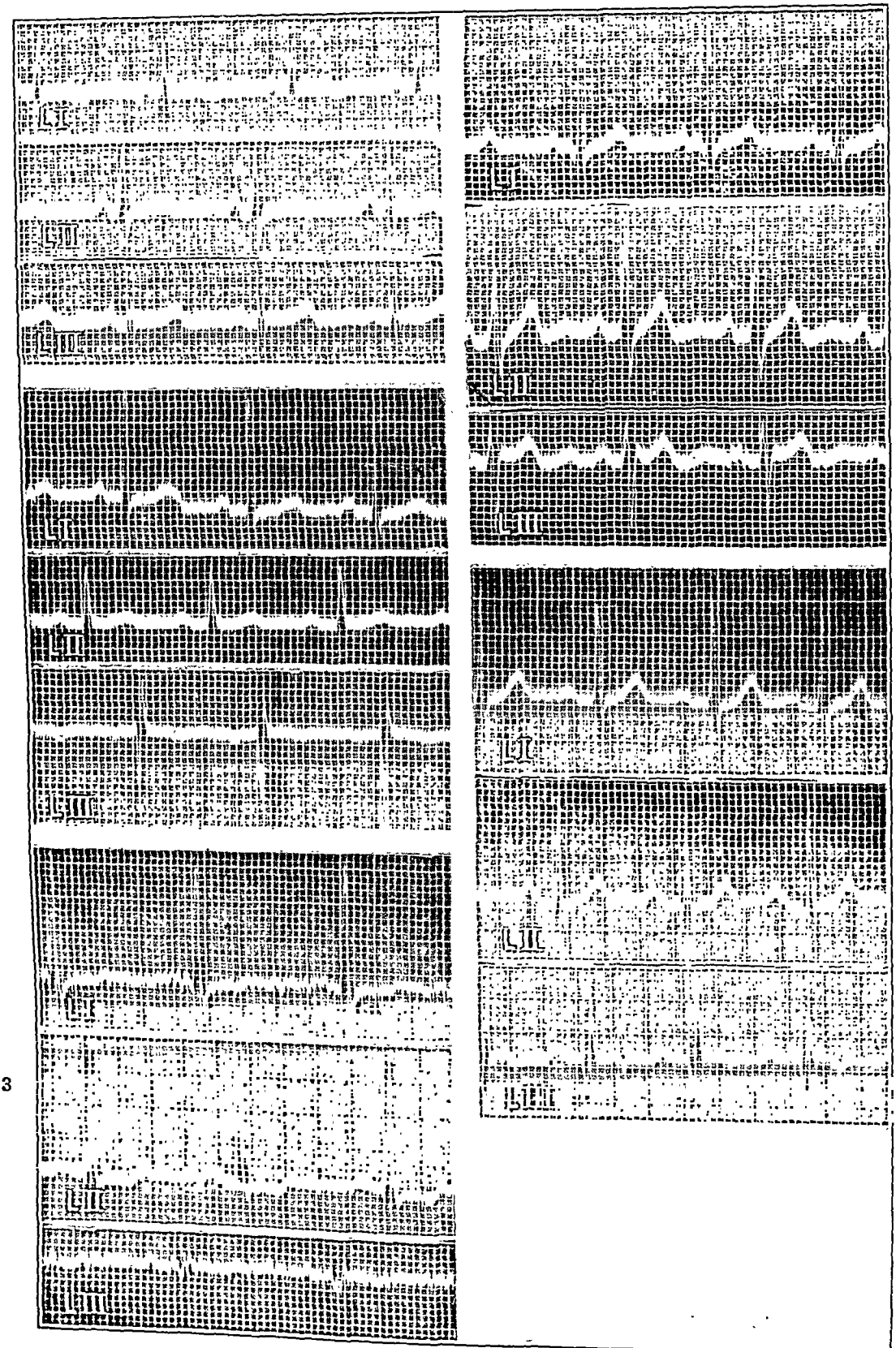
Fig. 1.—Case 1. Lead 1, slurring of upward deflection of *Q R S*; inverted *T*. Lead 2, slurring of upward deflection of *Q R S*; diphasic *T*. Lead 3, slurred *Q R S* complex and low voltage. Diagnosis: Myocardial damage.

Fig. 2.—Case 2. Lead 1, normal. Lead 2, normal. Le ad3, deep *Q*; inverted *P*; inverted *T*. Diagnosis: Normal tracing.

Fig. 3.—Case 3. Lead 1, deep *S* wave; depressed *S T* interval; diphasic *T*. Lead 2, depressed *S T* interval; diphasic *T*. Lead 3, inverted and notched *Q R S*, low voltage; inverted *T*. Diagnosis: Myocardial damage.

Fig. 4.—Case 4. Lead1, normal. Lead 2, deep *S*; tall *T*. Lead 3, inverted *Q R S*. Diagnosis: Left axis deviation. Taken May 12, 1932.

Fig. 5.—Case 5. Normal tracing.



FIGS. 1, 2, 3, 4 AND 5.

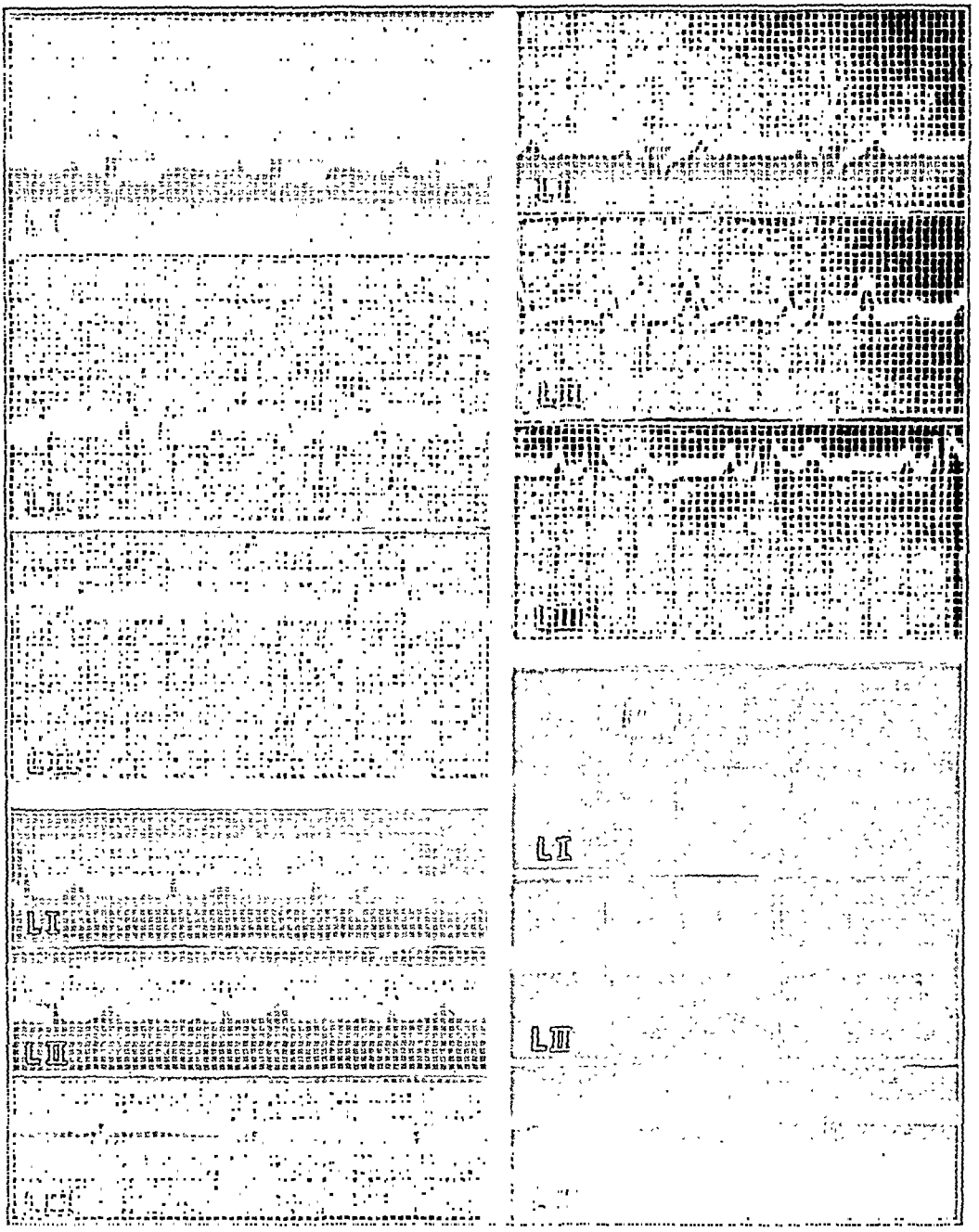


FIG. 6.—Case 6. Lead 1, diphasic T; depressed $S\ T$ interval. Lead 2, depressed $S\ T$ interval; deep S wave. Lead 3, diphasic P; inverted R; elevated $R\ T$ interval. Diagnosis: Myocardial damage. Taken November 10, 1932.

FIG. 7.—Case 7. Leads 1, 2 and 3 show slurring of the $Q\ R\ S$ interval; inversion of $Q\ R\ S$ interval in Lead 3; low voltage. Diagnosis: Myocardial damage.

FIG. 8.—Case 8. Lead 1, low take-off of $S\ T$. Lead 2, deep S and high T wave. Lead 3, high take-off of $S\ T$. Diagnosis: Myocardial damage.

FIG. 9.—Case 9. Lead 1, slurring of $Q\ R\ S$. Lead 2, slurring of $Q\ R\ S$; deep S wave. Lead 3, slurring of $Q\ R\ S$. $Q\ R\ S$ inverted; T inverted. Diagnosis: Myocardial damage; left axis deviation.

prompt and very marked alleviation of his coronary symptoms, a condition which has persisted to date. On October 18, 1934, we wished to determine whether the cessation of insulin would be attended by a return of his symptoms. We thus discontinued his insulin and left him on the same diet. Within a few days there recurred all his previous anginal complaints and at the same time he showed a break in sugar tolerance. The patient was put back on insulin, on November 30, and to date has again been free of anginal symptoms.

CASE 5.—Eva P., aged 54, housewife, gave a 4-month history of pruritus vulvi, polyuria, polydipsia, weakness and weight loss and frequent attacks of severe precordial pain for 7 months. Examination disclosed evidence of a hypertensive heart. Electrocardiogram (Fig. 5) showed no evidence of myocardial damage. Blood pressure was 165/90. Because she refused to take insulin she was given a restricted diet consisting of C., 90, P., 40, F., 40, on which she excreted 20 gm. of sugar in 24 hours, and her fasting blood sugar was 220 mg.%. For almost a year her anginal symptoms persisted and were elicited by slight exertion and emotional excitation. When she was finally persuaded to use insulin, she was given a diet containing C., 150, P., 50, F., 50, with 10 units of insulin once a day and an additional 15 gm. of available glucose 2 hours after the insulin. Besides the marked improvement in her diabetic symptoms, her stenocardial syndrome has almost entirely disappeared.

CASE 6.—Eva H., aged 62, housewife, had diabetes for 20 years. On her first visit to our clinic, in June, 1931, she was found to be a moderately severe diabetic. On a diet consisting of C., 120, P., 50, F., 65, with 20 units of insulin, b. i. d., she excreted 13.5 gm. of sugar in 24 hours and her fasting blood sugar was 240 mg.%. On September 17, 1931, she began to complain of frequent attacks of precordial pain. She had a hypertensive type of heart, enlarged to the left and a systolic murmur over the precordium. Her blood pressure was 180/100. Her anginal symptoms had progressively increased in frequency and severity, and on November 10, 1932, electrocardiogram showed left axis deviation with myocardial damage (Fig. 6).

Her insulin was then increased to 50 units a day in 3 divided doses with a diet containing 190 gm. of available glucose and adequate protection against hypoglycemic attacks. Since the increase in insulin and carbohydrate, there has been a very marked improvement in her anginal symptoms, although she still has occasional but mild episodes.

CASE 7.—Fannie L., aged 62, housewife, was admitted to the clinic on July 17, 1934, complaining of the classical symptoms of diabetes—polyuria, polydipsia, polyphagia, weakness and weight loss of 4 months' duration. In addition, she also complained of headaches, vertigo, dyspnea, palpitation and attacks of precordial pain. Examination disclosed an elderly woman, weighing 140 pounds, with manifestations of hypertensive heart. Her blood pressure was 215/90. It was found that she was a mild diabetic, for on a diet of C., 115, P., 65, F., 40, she excreted only traces of sugar and her blood sugar was 148 mg.%. Electrocardiogram showed evidence of myocardial damage and left axis deviation (Fig. 7). In view of her persistent precordial attacks, it was decided to increase the carbohydrate value of her diet by giving her C., 160, P., 60, F., 50, and 10 units of insulin once a day. She has been singularly free of anginal attacks since she started taking insulin.

CASE 8.—Sarah L., aged 66, housewife, was first seen, November 5, 1934, complaining of weakness, weight loss, polyuria and polydipsia and a history of having diabetes for 13 years. She also complained of frequent severe anginal pains radiating down the left arm for the past 5 years. Examination revealed evidence of weight loss, a hypertensive heart, sounds of poor quality and a ringing aortic sound. Blood pressure was 190/90. Electro-

cardiogram showed evidence of myocardial damage (Fig. 8). On a diet containing C., 150, P., 60, F., 75, she spilled 12 gm. in 24 hours. She was given 15 units of insulin once a day. There has been remarkable relief of her precordial symptoms in the face of the severe myocardial damage.

CASE 9.—Frieda B., aged 58, housewife, was first seen, September 8, 1930, complaining of marked weakness, polyuria, dryness of tongue, sleeplessness, headaches and frequent attacks of precordial pressure with palpitation and dyspnea, especially brought on by slight exertion. She had lost 40 pounds since the onset of her diabetes, 6 years ago. Examination disclosed a middle-aged woman, considerably wasted, evidence of hypertensive cardiac hypertrophy (confirmed by a 6-foot chest plate). There was a soft systolic blow over the base of the heart and a metallic accentuation of the aortic second sound. Her blood pressure was 210/110. She was excreting 40 gm. of sugar in 24 hours and her fasting blood sugar was 333 mg.%. Electrocardiogram (Fig. 9) showed evidence of myocardial damage. The patient was placed on a diet containing 225 gm. of available glucose, with 40 units of insulin in 2 divided doses. For the past 4 years she was maintained on this regimen, her weight has increased 15 pounds, she is always excreting between 5 and 10 gm. of sugar daily and her fasting blood sugars fluctuate between 200 and 270 mg.%. Although she still experiences symptoms of angina pectoris, they occur at relatively infrequent intervals and of a definitely milder order.

CASE 10.—Mitchell F., aged 43, discovered that he was diabetic in 1925. When seen, in June, 1927, he had no symptoms and examination disclosed a poorly nourished individual weighing 125 pounds, showing no other abnormal physical findings. He was then excreting traces of sugar and his fasting blood sugar was 160 mg.%. Blood pressure was 110/60. He was given a diet of C., 100, P., 60, F., 150, and no insulin. He was symptom-free until June, 1931, when he started to complain of attacks characterized by precordial pain and pressure radiating down both arms, paresthesias of the fingers, and dyspnea. These attacks were brought on by exertion and were relieved by rest. Examination of the heart disclosed no abnormalities. Blood pressure was 118/90. His urine was free of sugar and his fasting blood sugar was 164 mg.%. One year later he returned for another examination, at which time he reported that his anginal symptoms were becoming progressively worse and of greater frequency. He disclosed a definite break in sugar tolerance and his fasting blood sugar was 204 mg.%. Examination of his heart showed no abnormalities. His blood pressure was 128/86. His electrocardiogram was entirely normal. Teleoroentgenogram showed a heart normal in size, shape and position. A diagnosis was made of angina pectoris without coronary damage. He was then given a high carbohydrate diet consisting of C., 200, P., 60, F., 100, with 15 units of insulin twice a day. His diabetes was promptly controlled, for he excreted traces of sugar and his fasting blood sugars remained between 118 and 141 mg.%. He has been under observation for 3 years on a high-carbohydrate-insulin régime, during which time he has gained 7 pounds. He states that his anginal symptoms occur only rarely, are milder and are without radiations. His general well-being is much improved and he is able to engage in much more physical activity than he did before.

Discussion. In the consideration of the use of insulin as a therapeutic agent, the following principles were employed to protect the patient against even the mildest form of hypoglycemic reaction:

1. *Dietetic Control.* The caloric value of the diet was equivalent to the total energy requirements of the body and was computed on the basis of the sum of the basal heat production, the specific

dynamic action of the foodstuffs plus an estimated percentage of the basal metabolism to allow for activity. No attempt was made to reduce overweight patients because it was felt that a reducing diet would require too severe a restriction in carbohydrates.

Protein was given in the proportion of 1 gm. per kilo. of body weight. The amount of carbohydrate administered, influenced by our desire to give the patient an amount equal to the lower limits of what the normal person takes, that is, 250 gm., was never less than 3 gm. of carbohydrate per kilo of body weight. The fat was established by subtracting the caloric value of the protein and carbohydrates from the total calories and dividing the figure by 9, which is the caloric value of a gram of fat.

2. *Insulin.* Insulin was started in small test doses which were gradually increased up to the point where the sugar entirely disappeared from the urine or appeared only in traces. Blood sugars were not used as a criterion for the control of the diabetic state. It was felt that if a diet containing 200 or 250 gm. of available glucose could be taken care of by the organism without losing any in the urine, that the glucose was being either burnt or stored and that both these phenomena would relieve the clinical picture of this metabolic disorder.

3. *Further Dietetic Measures.* Realizing that the duration of the insulin effect in its depression of the blood sugar is in direct proportion to the dose of insulin, we instituted a routine protective procedure of giving our patients 15 gm. of readily absorbable carbohydrate (preferably in the form of fruit juice) 2 hours after the dose of insulin, which is the time when insulin shock is most likely to occur. We found this procedure so important that we routinely order the postcibal carbohydrate in all diabetics who take insulin. Since that is the time when the patient is experiencing a maximal insulin effect, we feel that this carbohydrate can be given with impunity. The result has been that hypoglycemic attacks have become an extreme rarity among our patients.

Some of these patients who were suffering from symptoms of coronary disease have been free of attacks for as long as 2 years since starting treatment. No attempt is being made to show that the use of insulin cures angina in these patients. Although the syndrome has entirely disappeared in many patients, others have been greatly relieved. None has been made worse by its use. We feel that this favorable clinical outcome is the result of having protected our patients against toxic insulin symptoms as manifested by hypoglycemic attacks.

These observations are not in accord with the clinical reports of Parsonnet and Hyman,[16] who have indicated that anginal symptoms are frequently aggravated in the insulin-treated cases even when the blood sugars are normal. They suspected that insulin has a toxic effect upon the myocardium regardless of its relationship to

the metabolism of glucose. On examination of their protocols, it will be seen that the blood sugar determinations were made several hours and even the following day after the attack of coronary thrombosis occurred. In some of the patients, glucose had been administered in the *interim*. We feel that these values have little significance regarding the content of sugar in the blood at the time the coronary episode occurred. Soskin and his co-workers feel that cardiac impairment, which both clinically and electrocardiographically resembles that produced by insulin hypoglycemia, may be produced in the elderly diabetic by giving therapeutic doses of insulin over a long period of time in spite of the fact that the blood sugars may be within the usually accepted normal range. An examination of their protocols reveals a condition, however, which does not warrant such conclusions. In citing their case of Harry S., for example, they record the fact that in spite of his maintaining an average blood sugar of 80 mg.%, while taking insulin, he showed electrocardiographic changes and cardiac symptoms similar to what they could produce in this patient by voluntarily eliciting a hypoglycemic attack. A detailed record of this patient's blood sugars on different days shows as follows: 61, 53 and 133 mg.%. Of course they will average 80 mg.%, but it is the cardiac picture which is created by a depression in the blood sugar to 61 and 53 mg.% that tells a clearer story. These are obviously hypoglycemic levels. Using the average of several figures, among which is included a high blood sugar, can only create an erroneous impression. It would be of considerably greater importance to determine the sugar content of the blood 3 and 4 hours after insulin has been injected in order to decide whether the patient is hypoglycemic. It is the lack of this type of observation that has led to what we consider false conclusions.

We feel also that a great deal of harm has been done by introducing the concept that insulin has a deleterious effect upon the heart of the elderly diabetic. It is unquestionably the hypoglycemic attack which is fraught with danger, but if it is possible to obviate the toxic effect of this hormone, why discard it as dangerous? Insulin is a double-edged sword much like any other powerful drug or hormone. Given in therapeutic doses it produces remarkable therapeutic effects; given in toxic doses it can even kill. But so is it true of morphin; one may give $\frac{1}{4}$ gr. for its desired effect and one may give 4 gr., enough to kill. Yet no one would think of eliminating morphin from his armamentarium because 4 gr. is a poison.

Conclusions. 1. The use of insulin in the diabetic suffering from angina pectoris and coronary sclerosis is discussed.

2. Insulin, like any other pharmacologic substance may be a toxic or a therapeutic agent, depending upon the manner of its use.

3. Methods for adequately protecting patients against the toxic effects of insulin are presented.

4. Insulin has been found to have a remarkable therapeutic value for the relief of cardiac pain of the diabetic.

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PRESENT VIEWS OF CALCIUM-PHOSPHORUS METABOLISM.*

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It is impossible to discuss the lesions resulting from abnormalities of calcium-phosphorus metabolism until the normal metabolism of these substances is known or hypothesized. The present state of our knowledge of calcium-phosphorus metabolism is so incomplete that it becomes necessary to construct from known data a workable hypothesis. This paper will attempt the elaboration of such an hypothesis from reported experimental and clinical data and from the results of personal investigation.

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Calcium and phosphorus enter the body by way of the diet. The normal daily intake of calcium is approximately 1 gm. and of phosphorus 2 gm. Although a normal amount of calcium and phosphorus may be ingested, yet this does not assure the assimilation of these elements and their entry into the body economy. Not only must an adequate supply of each element be present in the diet, but there must exist the proper quantitative proportion between calcium and phosphorus. The existence of a disproportion between the two is frequently as harmful as an absolute lack of either. Calcium should be in relation to phosphorus 1 to 1.5 or 1 to 2. Excessive dietary phosphorus, by forming insoluble compounds with the calcium of the diet, will markedly reduce the amount of calcium possible of absorption.

Quite frequently a large proportion of these elements occurs in the diet in insoluble forms and their assimilation by the gastrointestinal tract is consequently impossible.

The local conditions existing within the lumen of the small intestine may aid or deter the assimilation of calcium and phosphorus. Soluble salts of calcium may be thrown out of solution by the presence within the small intestine of excessive amounts of the carbonates of the digestive juices. The presence of excessive amounts of phosphates may act similarly; and a marked alkalin reaction of the intestinal contents may also precipitate soluble calcium salts and render them unassimilable. In the presence of large amounts of free fatty acids soluble calcium compounds are rendered insoluble through saponification. In consequence, excessive dietary fat, or the inability of the patient properly to digest the normal fat content of his diet (celiac disease) will, by rendering the dietary calcium insoluble, reduce the amount of this element available for assimilation.

Contrasted to these deterrent factors, assimilation of calcium and phosphorus is augmented by an adequate supply of vitamin D; by an acid reaction of the intestinal contents; and by a systemic acidosis—such as may be produced by the administration of ammonium chlorid.

The amount of ingested calcium phosphorus which is daily absorbed from the small intestine is not known but apparently varies widely in various individuals and at different times within the same individual. The quantitative intake of calcium and phosphorus may be quite adequate, but through faulty assimilation the amount of these elements reaching the tissues of the body may be inadequate.

Naturally those portions of the ingested calcium and phosphorus which are not assimilated are excreted. To this excretion of the unassimilated calcium and phosphorus must be added that portion of these elements which are thrown out from the blood stream. Normally 90% of the excretion is by way of the feces and 10% by

way of the urine. In normal adults the total amounts excreted in 24 hours, as estimated in periods of days, are slightly less than the amounts of these elements ingested during the same period of time.

Calcium and phosphorus assimilated from the small intestine enter the plasma of the blood. The total calcium content of the serum is normally in a concentration of 10 mg. % and inorganic phosphorus in a concentration of 4 mg. %. In a chemical sense the blood serum content of calcium is regarded as a saturated solution; certainly as regards neutral calcium phosphate the serum is saturated. The blood serum, however, does not behave in the unstable manner expected of a saturated solution.

The total blood serum calcium is divided into three fractions:

(*a*) The first fraction represents a loose colloidal combination with serum protein. This fraction totals approximately 4 mg. %, is physiologically inactive and comprises the fraction which is most stable and undergoes the least fluctuation in concentration.

(*b*) The second fraction represents a chemical combination of calcium with phosphorus in the form of a salt solution. The concentration of this fraction amounts to approximately 4 to 5 mg. % and is physiologically active. It is believed that the solution of this fraction is maintained through the intermediary action of parathyroid hormone and, according to Aub, brings the normal blood serum level of calcium above the renal threshold for this element and maintains it there.

(*c*) The third fraction, amounting to 1 to 2 mg. %, is present in the form of ionized calcium and is physiologically active.

Of the above three fractions, the last two are in equilibrium with phosphorus. Of the total calcium in the blood serum but 40 to 60% is diffusible.

It is important that the various fractions of blood serum calcium be determined. Abnormality of calcium metabolism is reflected more promptly in variations of the quantitative amount of either the ionized fraction or the second fraction, that held in solution through the action of parathyroid hormone. It is necessary to determine the total amount of blood protein, and consequently of protein metabolism, so that the calcium fraction in colloidal combination with the serum protein may be accurately known.

There is a demonstrable reciprocal relationship between the calcium and phosphorus content of the blood serum. If one rises, the other must fall if they are to remain in solution. Phosphorus exercises an important control in the maintenance of calcium solubility in the blood serum. The attempt is made to maintain the calcium-phosphorus concentration within the blood serum at a normal level. If it is not possible to obtain additional molecules from the diet, then the deposits in the bones will be drawn upon. Alteration in the normal concentration of these elements within the blood serum, resulting from abnormalities of excretion, vitamin D

content, or parathyroid hormone secretion, are not to be considered at this point.

It is possibly correct to regard the blood serum, calcium and phosphorus as being in a state of transportation either to or from the body tissues. It seems quite unlikely that the blood itself, although a circulating tissue, is actively engaged in the metabolism of these two elements. (This view is open to criticism.) The calcium and phosphorus of the blood serum are carried to the various organs and tissues of the body to perform their allotted functions.

Soluble calcium salts (by converting prothrombin into thrombin) are essential to the clotting of blood. Calcium is essential for the contractibility of involuntary muscle and for the maintenance of a normal degree of neuromuscular irritability. It also exerts a dominant rôle in maintaining the selective permeability of the living cell. Phosphorus is essential to lipoid metabolism, to the energizing of muscular contraction, and, in an unknown manner, is apparently essential to the functioning of nerve tissue. As approximately 99% of the body calcium is present within the bones, the most important function of these two elements consists in their deposition within the skeletal system of the body. Particularly is this true in the young and growing individual, as the strength and integrity of the bones depends upon the adequate performance of this function.

The manner in which calcium and phosphorus are removed from the blood stream, pass to the tissue fluids and are finally deposited in the form of tricalcium phosphate within the osteoid tissue of bones, comprises one of the great gaps in our knowledge of the metabolism of these two elements. There are two views regarding the manner in which calcium and phosphorus permeate and are precipitated in osteoid tissue. One is that this transportation and precipitation takes place through the medium of specific cells—the osteoblasts; the other view holds that the permeation and precipitation is one of a chemical nature and is, for the most part, independent of cellular activity.

Two substances play an important part in the precipitation of these elements in the osteoid tissue. The first is the enzyme *phosphatase* which, being the product of cellular activity, is probably elaborated, in varying degrees, by all cells of the body. The second substances, vitamin D, plays a most important part in this precipitation. Attention should be called, at this point, to the fact that vitamin D is supplied from two sources: (1) Through the diet; (2) through elaboration within the body of the individual. In the second case certain of the ultraviolet rays of the sunlight, act upon cholesterol-like compounds within the skin of the individual. These compounds, through the action of the ultraviolet rays, undergo a spatial rearrangement of their molecules and are transformed into vitamin D.

Phosphatase is possibly activated by vitamin D, and through enzymic action, has, according to Kay, the power of converting the

calcium-phosphate esters of the blood into insoluble tricalcium phosphate which is precipitated as such in the osteoid tissue. Such precipitation is aided by an alkalin balance or by an increase of the local phosphorus. Calcification is also found to vary inversely to the blood volume flow.

Calcium occurs in the bones in the proportion of 3 molecules of tricalcium phosphate to 1 molecule of calcium carbonate. This proportion persists regardless of whether calcium is being deposited or withdrawn from the bone. (75% of the ash of the entire body and 85% of the mineral matter of the bones is composed of calcium phosphate.)

Although calcium is deposited in all parts of the bony skeleton, Aub has shown it can be most easily mobilized and withdrawn from the spongiosa of the long bones. Such arrangement permits of the normal withdrawal of necessary amounts of calcium with a minimum impairment of the structural strength of the bones. It seems likely that calcium may be withdrawn from these depots more readily than it can be obtained by assimilation from the diet. Such limitation does not hold when pathological decalcification is operative.

Sight must not be lost of the fact that but two tissues normally calcify—bone and teeth. Experimentation has shown that these two tissues are the only ones which will undergo *in vitro* calcification. The calcification so produced closely resembles *in vivo* calcification. It must hence be concluded that bones and teeth possess over all other tissues a specific affinity for the calcium-phosphorus combination.

OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF VITAMIN B (B_1) TO POLYNEURITIS IN THE ALCOHOL ADDICT.*

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It is well known that alcohol addicts who consume little food often develop marked neurologic changes, whereas those who eat well, and in whom assimilation is not impaired by gastro-intestinal

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or hepatic disorders, rarely develop neurologic symptoms. Prior to the realization of the rôle played by the vitamins, it was thought that a full diet prevented the direct neurotoxic action of alcohol. That vitamin deficiency may be a factor in the development of polyneuritis in the alcohol addict was first mentioned, on theoretical grounds, by Shattuck[1] in 1928, and by Minot[2] in 1929; but Wechsler[3] was the first to analyze qualitatively the dietary histories of alcohol addicts with polyneuritis. He concluded that avitaminosis played a definite, and possibly the decisive, rôle in the production of polyneuritis. Meyer[4] also studied several alcohol addicts, with the concept of avitaminosis in mind, and came to similar conclusions. Following Wechsler's preliminary report Minot, Strauss and Cobb[5] analyzed qualitatively the diets of 43 alcohol addicts with polyneuritis. In 41 subjects the diet was considered inadequate. They stressed the importance of the inadequate food intake, and the rôle played by disorders of the gastro-intestinal tract in conditioning the assimilation and utilization of the accessory food factors. They pointed out the similarity of the manifestations of beriberi and polyneuritis in the alcohol addict, and suggested a common etiologic factor, namely, the lack of vitamin B. Strauss,[6] in 1935, gave a pint to a quart of blended whiskey daily to each of 10 alcohol addicts with polyneuritis; in addition a vitamin-rich diet was given, supplemented by the oral administration of 18 gm. of Vegex or 90 gm. of brewer's yeast, and 10 cc. of a vitamin B_1 concentrate administered parenterally, with 10 cc. of liver extract parenterally at weekly intervals. On this régime Strauss observed that the peripheral neuritis improved as rapidly with alcohol as without it. From this evidence he concluded that ingestion of whiskey had no demonstrable toxic effect on the peripheral nerves.

From the above literature on the etiology of polyneuritis in alcohol addicts it has been demonstrated:

1. That the alcohol addict with polyneuritis has as a rule a qualitatively inadequate food and vitamin intake.[3, 5]

2. That assimilation or utilization of the accessory food factors is often impaired by gastro-intestinal or hepatic disorders.[3, 5]

3. That the clinical manifestations and the pathologic findings of "alcoholic" polyneuritis and beriberi are remarkably similar.[5]

4. That ingestion of large amounts of whiskey, when accompanied by a vitamin-rich diet, supplemented by vitamins administered parenterally and per os, has no direct neurotoxic action.[6]

To complete the evidence, however, that polyneuritis* in the alcohol addict is due to the lack of vitamin B, the following postulates should be fulfilled: 1. It should be shown that the diet consumed by alcohol addicts with polyneuritis failed quantitatively, and over

* We are cognizant of the fact that there are other etiologic factors than avitaminosis B that may cause polyneuritis. These may and do operate in the alcohol addict as in subjects not addicted to the use of alcohol.

a sufficient period of time, to contain adequate amounts of vitamin B as compared with the normal requirement. 2. It should be shown that the diet consumed by alcohol addicts without polyneuritis, though the addiction was of long duration, contained quantitatively adequate amounts of vitamin B. This paper reports a series of quantitative observations bearing on the above points.

The vitamin B requirement of man has been estimated by Cowgill[7] from data on mice, rats, pigeons and dogs by the following formula:

$$\frac{\text{VITAMIN B mg. equivalent}}{\text{CALORIES}} = 0.0000284 \text{ WEIGHT in gm.}$$

We have applied Cowgill's method in a quantitative study of the diets of alcohol addicts to estimate their vitamin B and caloric intake. The values thus calculated were compared first, with the predicted requirement, and second, with the neurologic changes exhibited by these subjects. Cowgill has tested his formula by computing the vitamin B and caloric content of numerous human diets, associated and not associated with beriberi, and found a close agreement between the theoretical requirement predicted by his formula and the presence or absence of the disease. Examination of the Cowgill formula indicates that the vitamin B requirement is proportional to both the caloric intake and the body weight. From the nature of the equation, the expression

$$\frac{\text{VITAMIN B mg. equivalent}}{\text{CALORIES}}$$

(hereafter referred to as the VIT/CAL ratio) may be used as a quantitative expression, by reference to Cowgill's prediction chart,[7] of the adequacy or inadequacy of the vitamin B content of the diet of an individual of known weight. Cowgill uses caloric intake to express for practical purposes the energy exchange of an individual. The almost complete utilization by man of moderate amounts of alcohol is well known.[8] The energy exchange, however, calculated for practical purposes from the caloric intake, may not reasonably indicate the calories utilized when large quantities of alcohol are consumed, since under these conditions significant portions of alcohol may be excreted unchanged through the lungs and kidneys, or lost by vomiting and diarrhea. Moreover, the metabolic limits of the body to burn alcohol may be exceeded in subjects consuming more than a pint of whiskey daily, since Mellanby[9] has calculated that the average man can oxidize but 10 cc. of alcohol per hour.

The importance of the calories derived from alcohol in relation to vitamin B requirement can be illustrated by using Cowgill's calculation of the VIT/CAL ratio of Sherman's[10] average American diet. This diet contains 6847 mg. eq. of vitamin B and 2500 calories, and gives a VIT/CAL ratio of 2.74. This ratio, by reference to Cowgill's prediction chart, is adequate for a 96 kg. man. An indi-

vidual who supplements this diet by one pint of whiskey daily adds about 1600 calories to the denominator of the equation. The VIT/CAL ratio now becomes 1.67, which is adequate for a 60 kg. man. An individual weighing more than 60 kg. on this vitamin B and caloric consumption would, theoretically, in time show evidence of a vitamin B deficiency.

To calculate the VIT/CAL ratio of the diets of our subjects we used Cowgill's[7] Vitamin B (B_1) Index of Foods, which also lists the caloric values. Average portion weights[11] were used to estimate the consumption in grams of portions of various foods consumed. Fortunately for our calculations the diets of confirmed alcohol addicts are as a rule monotonous and simple, and less error results in the estimation of these diets than in the determination of the VIT/CAL ratios of persons consuming a full, varied, and mixed diet.

The 42 subjects forming the basis of this study were tentatively selected on the probability of the patient giving an adequate and accurate history of the dietary and alcoholic intake. If the patient gave essentially the same history on several succeeding days (only about 1 in 10 alcohol addicts did this), and if from information given by friends or relatives the history seemed reliable, then the case was accepted for this study.* Two VIT/CAL ratios were calculated for each patient, one omitting (VIT/CAL without ALC.) and one including (VIT/CAL with ALC.) the calories derived from alcohol. In subjects consuming more than a pint of whiskey daily, a third ratio was calculated which included only the first 1600 calories derived from alcohol per diem as this is the probable maximum amount that can be oxidized (VIT/CAL + 1600). Each ratio was compared with the predicted requirement, and with the neurologic observations made before treatment was instituted. It is recognized that the alcohol addicts forming the basis of this study often manifested signs attributable to an avitaminosis other than B. At the present time, however, there is no method to estimate quantitatively the human requirement of these other vitamins. It was therefore impossible for us to correlate quantitatively the intake of vitamins other than B with the clinical findings in our subjects.

We have included in this study two groups of subjects: those definitely having polyneuritis and those definitely not having polyneuritis. Subjects included in the group having polyneuritis had at least absent ankle jerks and demonstrable sensory changes in the peripheral nerves. Most subjects in this group showed more than this minimal requirement. Subjects to be included in the group without polyneuritis had no changes in the deep reflexes and showed no sensory changes. Certain subjects showing changes

* In the sense that only alcohol addicts who gave reliable histories were included in this study our cases are selected. However, these cases represent consecutive subjects admitted to the Medical Service fulfilling the criteria for the diagnosis of polyneuritis who, according to our criteria, gave reliable histories.

falling between these two groups of criteria were excluded from the study.

TABLE 1.—SUMMARY OF OBSERVATIONS ON 26 ALCOHOL ADDICTS WITH POLYNEURITIS.

Case.	Sex.	Age.	Alcohol.		Food: average daily consumption in—		VIT/CAL ratios.				Neurologic involvement.		
			Time.	Average daily intake in calories.	Calories.	Vit. B mg. eq.	Without alcohol.	+ 1600 C.	With alcohol.	Cowgill's predicted requirement.	Polyneuritis.	Cord.	Brain.
258	M	51	1 Y	6,400	405	1,317	3.2	0.6	0.2	1.75	+	0	0
259	M	41	6 M	3,200	755	1,725	2.3	0.7	0.5	2.35	+	0	0
271	M	37	3 Y	1,600	330	923	2.8	0.5	0.5	1.80	+	+	+
273	M	50	25 Y	1,600	2,500	6,874	2.7	1.7	1.7	1.80	+	+	+
279	F	45	7 Y	1,600	833	2,286	2.7	0.9	0.9	1.25	+	+	+
280	M	57	3 M	6,400	888	1,845	2.0	0.7	0.3	2.00	+	0	0
295	M	59	10 W	1,600	673	1,020	1.5	0.4	0.4	1.70	+	0	0
297	M	38	2 M	1,600	1,250	3,423	2.7	1.3	1.3	2.00	+	0	0
300	M	53	3 M	4,800	357	978	2.7	0.5	0.2	2.15	+	+	0
324	M	48	6 M	1,600	965	3,130	3.2	1.2	1.2	1.85	+	0	+
327	M	43	2 M	6,400	0	0	0	0	0	2.20	+	0	0
333	M	40	2 M	4,500	0	0	0	0	0	1.90	+	+	+
335	M	52	2 M	800	756	1,624	2.1	...	1.0	1.71	+	0	0
336	M	56	33 D	4,800	863	2,431	2.8	1.0	0.4	2.35	+	0	0
339	F	45	2 Y	1,600	492	406	0.8	0.2	0.2	1.40	+	+	0
366	M	52	22 D	3,000	500	1,800	3.6	0.9	0.2	2.55	+	0	0
388	M	47	8 M	4,000	1,121	2,590	2.3	0.9	0.7	1.15	+	0	0
392	F	57	2 M	2,600	276	671	2.4	0.4	0.2	2.05	+	0	+
443	M	35	6 W	2,400	2,018	5,932	2.9	1.6	1.3	2.20	+	+	+
444	M	29	8 Y	3,200	1,809	5,774	3.2	1.7	1.1	1.80	+	+	+
457	M	38	2 M	3,200	1,102	3,825	3.5	1.0	0.9	1.70	+	0	0
458	M	54	15 D	3,200	555	1,107	2.0	0.5	0.3	2.10	+	0	0
459	M	46	20 D	3,200	726	3,355	4.6	1.4	0.7	2.10	+	0	0
467	M	45	3 W	4,800	0	0	0	0	0	1.85	+	0	+
468	F	47	10 Y	2,400	1,568	2,878	1.8	0.9	0.7	2.30	+	0	+
472	M	46	6 Y	2,400	720	3,000	4.2	1.3	1.0	1.60	+	0	0

Results. In line with the hypothesis that polyneuritis in the alcohol addicts is due to lack of vitamin B, we find that the diet consumed by those alcohol addicts with polyneuritis failed quantitatively, and over a sufficient period of time, to contain adequate amounts of vitamin B as compared with the predicted requirement. The evidence for this conclusion is presented in Table 1, which presents data on 26 subjects. It will be noted that in these alcohol addicts an adequate or an inadequate diet in respect to vitamin B as estimated by the VIT/CAL without ALC. ratio bears no relationship to the presence or absence of polyneuritis. In 18 subjects the diet alone was adequate when considered in relationship to the vitamin B requirement as calculated on the basis of food alone. Since, however, in these subjects a large percentage of the energy intake

was represented by alcohol, the calories obtained from this source should be included in the equation. When all the available calories are included (VIT/CAL with ALC. ratio) the vitamin B intake became in every instance inadequate. Since 18 of these 26 subjects consumed more than 1600 alcohol calories daily, and thereby probably exceeded the metabolic limits of the body to burn alcohol, the VIT/CAL + 1600 ratio may be the most representative ratio for this group. In the 18 subjects to whom this formula was applicable every one remained inadequate in vitamin B intake as judged by Cowgill's predicted requirement.

TABLE 2.—SUMMARY OF OBSERVATIONS ON 8 ALCOHOL ADDICTS WITHOUT POLYNEURITIS WHO MAINTAINED AN ADEQUATE VITAMIN B INTAKE.

Case.	Sex.	Age.	Alcohol.		Food: average daily consumption in—		VIT/CAL ratios.				Neurologic involvement.		
			Time.	Average daily intake in calories.	Calories.	Vit. B mg. eq.	Without alcohol.	+ 1600 C.	With alcohol.	Cowgill's predicted requirement.	Polyneuritis.	Cord.	Brain.
330	M	61	40 Y	450	2,500	7,890	3.1	..	2.7	2.25	0	0	0
334	M	64	40 Y	1,500	2,083	10,398	5.0	..	2.8	2.75	0	0	0
340	F	43	6 M	1,600	3,272	9,918	3.0	2.0	2.0	1.70	0	0	0
358	M	45	18 M	750	1,901	7,100	3.7	..	2.7	2.60	0	0	0
403	M	35	7 Y	800	5,021	17,784	3.5	..	3.0	2.67	0	0	0
417	M	55	10 Y	1,600	2,457	10,466	4.3	2.6	2.6	2.25	0	0	0
455	M	34	7 Y	1,600	2,868	12,102	4.2	2.7	2.7	2.00	0	0	0
466	M	54	10 Y	2,300	3,387	13,404	3.9	2.7	2.3	1.70	0	0	0

On the other hand, the diet consumed by alcohol addicts without polyneuritis, though the addiction was of long duration, contained quantitatively adequate amounts of vitamin B as compared with the normal requirement. The evidence on which this conclusion is based is given in Table 2, where data on 8 subjects without polyneuritis are tabulated. These subjects maintained an adequate intake of vitamin B even though they were on a daily consumption of alcohol varying from 450 to 2300 calories over periods ranging from 6 months to 40 years. In every instance the VIT/CAL without ALC. ratio exceeded by a substantial margin the predicted requirement, and even when the alcohol calories are included in the calculation the diet remained adequate in respect to vitamin B. Each of these subjects regularly included in their diets a food that provided exceptional amounts of vitamin B. Sherman's[10] average American diet was estimated by Cowgill to have a VIT/CAL ratio of 2.74. Each of these subjects maintained a VIT/CAL without ALC. ratio of 3 to 5. Subject 334, aged 64 years, has been a bartender since the age of 24. During this 40-year period his average consumption of

alcohol has consisted of 10 1½-ounce drinks of whiskey daily; the whiskey was placed in a 10-ounce bar glass which was then filled with whole milk, and in this way the patient obtained at least 75 ounces of milk daily. This amount of milk contains about 1500 calories and about 8100 mg. eq. of vitamin B. By adding the 1500 alcohol calories to the 1500 milk calories we obtain a VIT/CAL with ALC. ratio of 2.7. The additional food he consumed maintained his VIT/CAL with ALC. ratio at 2.85, which just exceeded his predicted requirement of 2.75. Subject 403 obtained an extremely high intake of vitamin B by eating regularly 5 eggs and 2 slices of ham for breakfast, and 2 pork chops and bean or pea soup for lunch. These foods are all exceptionally rich sources of vitamin B.*

TABLE 3.—SUMMARY OF OBSERVATIONS ON 8 ALCOHOL ADDICTS WITHOUT POLYNEURITIS WHO CONSUMED INADEQUATE AMOUNTS OF VITAMIN B.

Case.	Sex.	Age.	Alcohol.		Food: average daily consumption in—		VIT/CAL ratios.				Neurologic involvement.		
			Time.	Average daily intake in calories.	Calories.	Vit. B mg. eq.	Without alcohol.	+ 1600 C.	With alcohol.	Cowgill's predicted requirement.	Polyneuritis.	Cord.	Brain
325	F	35	14 D	1,600	2,500	6,800	2.7	1.6	1.6	1.70	0	0	0
359	M	52	7 D	3,200	112	100	0.9	0.06	0.03	2.30	0	0	0
363	M	63	14 D	4,800	0	0	0	0	0	2.15	0	0	0
357	M	20	18 D	3,200	640	2,199	3.4	1.0	0.6	2.35	0	0	0
402	M	30	6 M	1,600	2,165	7,413	3.4	2.0	2.0	2.10	0	0	0
413	M	50	10 D	2,400	638	2,000	3.1	0.9	0.7	2.40	0	0	0
438	M	48	21 D	6,400	412	660	1.6	0.3	0.1	1.80	0	0	0
456	M	48	2 M	3,200	1,445	5,667	3.9	1.8	1.2	1.80	0	0	0

The 8 subjects listed in Table 3 were all deficient in vitamin B intake as judged by the VIT/CAL with ALC. ratio. As judged by the VIT/CAL + 1600 ratio, 7 of these 8 subjects were deficient. The exception (Subject 456) had a borderline ratio. The protective factor in this group was the short duration of the alcoholic bout. In 6 of the 8 subjects the period of alcohol addiction did not last over 3 weeks. Subject 402 was on an alcoholic bout for 6 months with an average consumption of 1 pint of whiskey daily. His predicted requirement as judged by the VIT/CAL ratio was 2.1. The estimated VIT/CAL with ALC. ratio was 2, which falls within Cowgill's borderline range. Subject 456 was on an alcoholic bout for 2 months with an average consumption of 1 quart of whiskey daily. His predicted requirement by the VIT/CAL ratio was 1.8. The estimated

* Even if the error involved in the estimation of the diets of the subjects presented in Tables 1 and 2 were as high as 50%, the Vit/Cal+1600 ratio of only one subject (334) would conflict with our postulates.

VIT/CAL + 1600 ratio was 1.8. If all the alcohol calories are included, the estimated VIT/CAL with ALC. ratio becomes 1.2, which is definitely inadequate. This individual, as will be shown later, with this degree of vitamin B deficiency as measured by this latter ratio and over this period of time, would not with certainty develop polyneuritis.

The time required to produce clinical evidence of polyneuritis on a vitamin B deficient diet is variable. That the disease may develop in a short time is demonstrated by 4 subjects (458, 459, 366 and 336), all of whom had polyneuritis on admission following a period of vitamin B deficiency lasting 15, 20, 22 and 33 days, respectively. We were able to date accurately the duration in 3 of these subjects since they began their drinking bout on Christmas or New Year's Eve. The other subjects having polyneuritis were on a continuous daily consumption of whiskey varying from 6 weeks to 25 years. It is reasonable to assume that a subject having a VIT/CAL ratio equivalent to but 30% of the predicted requirement would develop clinical evidence of vitamin B deficiency earlier than a subject having 60% of the predicted requirement. Ohomori[12] found signs of nerve involvement as early as the 7th to 10th day on a diet estimated by Cowgill's method to be 36% adequate. We have estimated the number of days of complete 100% deficiency by multiplying the per cent deficiency by the number of days over which the deficiency occurred (hereafter referred to as "days of estimated absolute deficiency"). In 10 days Ohomori's subjects accumulated 6.4 days of estimated absolute deficiency of vitamin B. Frazer and Stanton[13] fed a diet 68% adequate as judged by the VIT/CAL ratio to a group of laborers whose average requirement was a ratio of 1.25. The first case of beriberi appeared on the 89th day, or following 28.5 days of estimated absolute deficiency. We have calculated the days of estimated absolute deficiency in each of our subjects. In those subjects using more than 1600 alcohol calories daily the VIT/CAL + 1600 ratio was used in the determination. Each subject with an estimated absolute deficiency of 21 days or more had polyneuritis. Since many subjects in this group may have had signs of peripheral neuritis for a variable length of time before observation, we have tabulated in Table 4 only the subjects who had estimated absolute deficiency for 21 days or less. Subject 459 developed polyneuritis after 6.6 days of estimated absolute deficiency, while Subject 438 showed no clinical evidence of polyneuritis after 17.4 days of estimated absolute deficiency. Polyneuritis was present in Subjects 458, 366 and 336 after 11.4, 14.3 and 19.1 days, respectively, of estimated absolute deficiency. It appears, therefore, that an individual may develop polyneuritis if the caloric need is satisfied by a diet free of vitamin B for a period of a week, while every individual in our series had polyneuritis if the period of estimated absolute deficiency was 21 days or more.

Subject 456, without polyneuritis, is the only possible exception to the rule that an alcohol addict with an inadequate vitamin B intake over a sufficient period of time will develop polyneuritis. This subject consumed a diet just adequate, as expressed by the VIT/CAL + 1600 ratio, and therefore, on this basis, is not an exception. If all the alcohol calories are included in the denominator of the equation (a procedure which we do not feel to be justified, as 1600 alcohol calories is the probable maximum amount metabolized within 24 hours), the VIT/CAL with ALC. ratio becomes 1.2, which is 33% less than his predicted requirement of 1.8. On this basis the deficiency lasted only 60 days, giving 19.8 days of estimated absolute deficiency. It appears that this duration of vitamin B deficiency will not with certainty produce polyneuritis.

TABLE 4.—CORRELATION OF DAYS OF ESTIMATED ABSOLUTE DEFICIENCY IN VITAMIN B AND POLYNEURITIS IN THE ALCOHOL ADDICT.

Subject.	Estimated deficiency in %.	Duration of deficiency in days.	Estimated absolute deficiency in days.	Polyneuritis.
325	6.0	14	0.8	0
413	63.0	10	6.3	0
459	33.0	20	6.6	+
359	96.0	7	6.7	0
402	5.0	180	9.0	0
357	57.0	18	10.2	0
458	76.0	15	11.4	+
363	100.0	14	14.0	0
366	65.0	22	14.3	+
438	83.0	21	17.4	0
336	57.0	33	19.1	+
467	100.0	21	21.0	+
297	35.0	60	21.0	+

Discussion. The etiology of polyneuritis in the alcohol addict is clarified by the quantitative estimation of the adequacy or inadequacy of the vitamin B intake of alcohol addicts. The fact that every alcohol addict with polyneuritis had a VIT/CAL with ALC. or VIT/CAL + 1600 ratio below the predicted requirement for this vitamin is in itself good evidence that the lack of vitamin B is the cause of the polyneuritis. This fact alone, however, is not direct and conclusive evidence. It is possible that the polyneuritis in the alcohol addict may be due to the direct toxic action of alcohol or even to the lack of another vitamin, such as vitamin A, as suggested by Mellanby,[14] and the inadequate intake of vitamin B may be coincidental because of anorexia. Evidence, in addition to that of Strauss,[6] that alcohol does not have a direct toxic action on the peripheral nerves is derived from the fact that no alcohol addict with an adequate vitamin B intake, as expressed by the VIT/CAL with ALC. ratio, had clinical evidence of peripheral neuritis. It is true that the group without polyneuritis but with an adequate vitamin B intake (Table 2) had an average per diem intake of whiskey less

than the group with polyneuritis. These subjects, however, drank an amount of whiskey sufficient to cause polyneuritis if alcohol *per se* were its cause. To illustrate this point, 4 subjects having VIT/CAL with ALC. ratios above the predicted requirement used whiskey over a long period of time without developing polyneuritis. Of these, 3 subjects (340, 417, 454) used 1 pint of whiskey daily for 6 months to 10 years, and 1 subject (466) used 23 ounces of whiskey daily for 10 years. That this is a sufficient intake of whiskey, and continued over an adequate period of time, to cause polyneuritis if alcohol had a direct neurotoxic action, is evidenced by the 3 subjects (297, 295, 335) with inadequate VIT/CAL with ALC. ratios who drank but 1 pint or less of whiskey daily for 10 weeks or less and developed polyneuritis. Subject 335, with an inadequate VIT/CAL with ALC. ratio, drank but ½ pint of whiskey daily for 2 months and developed polyneuritis. The 8 subjects with adequate VIT/CAL with ALC. ratios all drank ½ pint or more of whiskey daily for 6 months to 40 years without developing polyneuritis. It is therefore clear that in these subjects alcohol *per se*, even when used in large amounts over a long period of time, had no direct toxic action on the peripheral nerves.

The proof that polyneuritis in the alcohol addict and in beriberi are due to vitamin B deficiency rests upon the same evidence. Both diseases have been shown to occur only in subjects having a vitamin B intake less than their predicted requirement. Neither disease occurs in subjects having a vitamin B intake greater than their predicted requirement, unless their requirement is abnormally increased (fever, hyperthyroidism, pregnancy, diuresis) or assimilation is prevented (vomiting, diarrhea). Both diseases have similar clinical manifestations, and are characterized by similar pathologic findings. Both diseases, unless far advanced and the nerve lesions beyond repair, respond to adequate vitamin B therapy. We are therefore of the opinion that polyneuritis in the alcohol addict and beriberi are one and the same disease, and that both are due to the lack of vitamin B.

It is suggested that the alcohol addict, to prevent a possible polyneuritis, should consume a full mixed diet supplemented by about 250 mg. eq. (50 Sherman units) of vitamin B for each 100 calories of alcohol (about 1 ounce of whiskey) he consumes. This amount of vitamin B can be conveniently obtained in about 1 gm. of Vegex.

The lack of other accessory food elements, such as vitamin A, in association with the lack of vitamin B, as suggested by Mellanby,[14] does not seem to us to play a very decisive rôle in the production of polyneuritis in the alcohol addict. The vitamin A requirement of human beings at present is unknown. The estimation of the adequacy or inadequacy of the vitamin A intake in our subjects could be only conjecture. It is barely possible that each of our subjects deficient in vitamin B was also deficient in vitamin A.

This is not at all probable as in many of our subjects the period of alcohol addiction and food inadequacy was relatively short. Animals maintained on a diet deficient only in vitamin A require long periods of inadequacy before neurologic signs or symptoms become manifest. Conversely animals deficient in vitamin B develop neurologic changes relatively early. Polyneuritic signs in our subjects were always present after 21 days, and occurred as early as in 7 days of estimated absolute deficiency. This is probably too early to expect signs of vitamin A deficiency.

There was in our subjects no very clear correlation between the degree of vitamin B deficiency and the presence or absence of central nervous system involvement. In the 12 subjects showing central nervous involvement, 10 had an estimated absolute deficiency for 48 days or more. Subjects 443 and 467 showed signs of central nervous involvement after only 11.3 and 21 days, respectively, of estimated absolute deficiency. But other subjects may have an estimated absolute deficiency for longer periods of time without showing evidence of central nervous system involvement. Subjects, 472, 258 and 259, had 415, 240 and 126 days, respectively, of estimated absolute deficiency, but showed only peripheral nerve involvement. Although the changes in the central nervous system appeared clinically to be associated with vitamin B deficiency, there is clearly no correlation between the degree of deficiency of vitamin B and the presence or absence of spinal cord or brain involvement.

Summary. The vitamin B and caloric intake of 42 alcohol addicts, 26 of whom had polyneuritis, have been estimated quantitatively by Cowgill's formula. When the first 1600 calories contained in the alcohol consumed by each subject are included in the estimation of the VIT/CAL ratio, a definite correlation is found between the inadequacy or adequacy of the vitamin B intake and the presence or absence of polyneuritis. This correlation is as follows:

1. Every alcohol addict with polyneuritis had an estimated inadequate vitamin B intake.
2. No alcohol addict with an estimated adequate vitamin B intake had polyneuritis.
3. Every alcohol addict with estimated absolute deficiency of vitamin B for 21 days or more had polyneuritis.
4. Polyneuritis may develop in an alcohol addict as early as the 7th day of estimated absolute deficiency of vitamin B.

Our data substantiate the hypothesis that polyneuritis in the alcohol addict is due to the lack of vitamin B by demonstrating: (1) that the diet consumed by alcohol addicts with polyneuritis failed quantitatively and over a sufficient period of time to contain adequate amounts of vitamin B as compared with the predicted requirement; and (2) that the diet consumed by alcohol addicts without polyneuritis, though the addiction was of long duration,

contained quantitatively adequate amounts of vitamin B as compared with the predicted requirement.

It is therefore concluded that alcohol has no direct toxic action (chronic) on the peripheral nerves, and that polyneuritis in the alcohol addict is due to vitamin B deficiency.

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A STUDY OF THE DIURETIC EFFECT OF MERCUPURIN IN MAN.*

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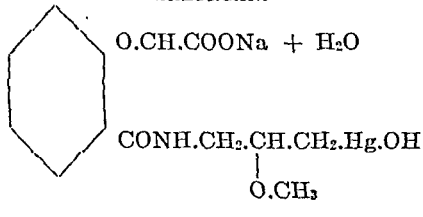
Since the introduction of novasurol as a mercurial diuretic by Saxl and Heilig,[1] in 1920, attempts have been made to vary the organic portion of the compound in its relationship to mercury in

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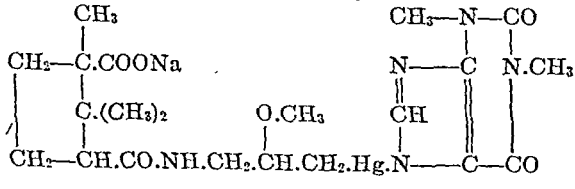
order to increase its efficiency and to decrease the general and local toxicity. Thus salyrgan, introduced in 1924 by Bernheim,[2] was found to have greater diuretic action and to be less toxic than novasurol.[3]

In 1928 v. Issekutz and v. Vegh[4] studied the diuretic action of numerous mercurial salts in rabbits and their toxicity in rats and found that preparation VI, a camphoric acid derivative, to be 10 to 15 times less toxic than sublimate and one-half as toxic as salyrgan. When combined with theophyllin, the diuresis was not only greater than that produced by salyrgan alone or salyrgan with theophyllin, but also retained the same relationship of toxicity as above. A combination closely resembling preparation VI was introduced clinically as novurit and is known in this country as mercupurin. This is a complex mercurial salt containing 5% theophyllin, 3.5% of which is claimed by the distributors[5] to be chemically bound to it. The essential differences between mercupurin and salyrgan can be seen from an examination of their chemical formulæ.

SALYRGAN.



MERCUPURIN.



The allylamid group, although alike in both preparations, separates the mercury from a cyclopentane in mercupurin, and from a benzol ring in salyrgan.

European investigators[6] in general have reported favorable clinical results with the use of mercupurin. In this country Crawford and McDaniel[7] obtained in every instance but one a greater diuresis with this drug than with salyrgan. On the other hand, although Fulton and Bryan[8] found that clinically mercupurin was an effective diuretic they concluded that no preference could be given to it over salyrgan.

The conclusion one reaches from a survey of the literature is that mercupurin seems to be an effective and probably a safe diuretic, but that there is still some doubt as to whether the presence of theophyllin in it makes it a more efficient diuretic than the simple mercurials.

The present study was planned to determine the efficiency and degree of safety of mercupurin as a diuretic in man and secondly to determine, if possible, whether the presence of theophyllin was necessary.

Methods and Results. Patients in congestive heart failure with considerable dependent edema were chosen for this study. All were kept on a preliminary control period of absolute bed rest before any diuretic was administered. The diet averaged 2700 calories and consisted of C. 240 gm., P. 90 gm., F. 108 gm. with a daily salt intake of approximately 5 gm. This salt content is considerably higher than that used by previous investigators. It has been shown that occasionally the effectiveness of a diuretic diminishes after its prolonged use, probably the result of depletion of the ions necessary to maintain ionic equilibria in the body.[9,10] There exists a definite relationship between the amount of fluid mobilized for diuresis and the amount of salt available in the body to be excreted. Since the salts of the urine, especially sodium chlorid, are increased with diuretics[9] and as sodium chlorid is a salt essential for life, the body takes necessary steps to prevent abnormal depletion of its concentration from the tissues.[9] Recently attention has been brought to the necessity of using an adequate diet ash in the treatment of edema of congestive heart failure.[11] For these reasons no restrictions were placed on the salt intake other than it should be constant from day to day.

Fluid was restricted to 1200 cc. daily. Patients were weighed at the same time each day on a scale which was accurate to 2 ounces and which was brought to the side of the bed. Those too sick to be weighed were not included in this report.

In the early stages of the study, urine output was measured but it soon became evident that it was more accurate to follow the daily weight curve because it fluctuated very much less during the control period. It is important to know the degree of edema present, as there is a definite relationship between the amount of fluid retained by the body and the subsequent diuresis. This point is well illustrated in Figure 1. The urinary output is not an indication of the amount of fluid that can be mobilized in the body for diuresis. The range between the weight before and after diuresis and the level attained when the patient is edema-free is the best indicator for the effectiveness of a diuretic that is available at the present time. Of course it must be understood that loss in weight due to factors other than loss of edema must be controlled. For this reason those patients who could not be controlled as to diet, use of cathartics, vomiting, or any other factor which would influence body weight other than edema of congestive heart failure were excluded from this study.

Twenty patients were studied under controlled conditions. When the weight was constant or increasing after a control period, the

patient was given the diuretic. In those receiving digitalis the diuretic was not given until the patient was completely digitalized and the weight constant on a maintenance dosage. In all cases frequent urine specimens preceding and following each injection were examined especially for red blood cells. The intravenous route was used except in three instances when the drug was given intramuscularly.

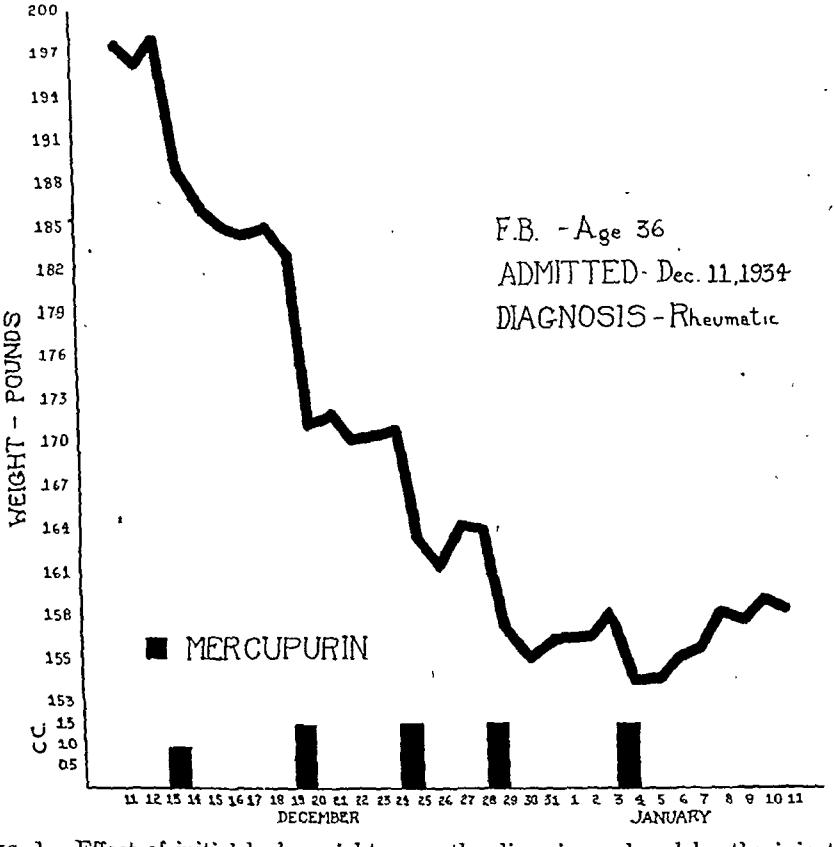


FIG. 1.—Effect of initial body weight upon the diuresis produced by the injection of mercupurin (Case 4, Table 1).

In Table 1 are shown the results of the administration of mercupurin in 10 patients. In every instance a significant weight loss occurred. Diuresis usually began within 4 hours and lasted more than 1 day. In 2 cases it appeared to initiate a diuresis which lasted as long as 4 days. Diuresis was considered complete when the patient stopped losing weight. The greater the amount of edema (as indicated by the patient's weight) the greater the weight loss. In 2 cases, 3 and 5, to whom ammonium chlorid was given, an increased diuresis was obtained even though the patients were on a lower initial weight level. This is in agreement with observations of a number of investigators with other mercurial diuretics. In

no case was there any evidence of a toxic action on the kidney. It is evident from a study of these 10 cases that mercupurin is an efficient and safe diuretic.

TABLE 1.—SHOWING THE DIURETIC EFFICIENCY OF MERCUPURIN (M).

Case No.	Case.	Diuretic cc.	Date.	Amm. chlorid, gm.	Initial wt.	Wt. first day.	Loss first day.	Max. loss.	Days required for wt. loss.
1	J. W.	M.—2.0	8/30	..	150½	138½	12	12	1
		M.—1.0	9/7	..	143	139	4	4	1
2	C. W.	M.—2.0	8/28	..	106	98	8	18	2
3	G. D.	M.—2.0	8/28	..	180½	174½	6	6	1
		M.—2.0	9/1	..	175	170½	4½	7	3
		M.—2.0	9/5	..	169	167½	1½	2½	3
		M.—2 0	9/14	5.4	166½	151½	15	17½	2
		M.—2.0	9/18	5.4	155	145	10	10	1
4	F. B.	M.—1.0	12/13	..	198	189	9	14	4
		M.—1.5	12/19	..	183	171	12	13	2
		M.—1.5	12/24	..	170½	163	7½	9½	2
		M.—1.5	12/28	..	164	157	7	9	2
		M.—1.5	1/3	..	158	153½	4½	4½	1
5	B. J.	M.—1.0	12/15	..	144	141	3	8	4
		M.—2.0	12/18	..	136	135	1	6	3
		M.—2 0	12/22	5 4	131	128	3	6	4
		M.—2.0	12/27	5.4	127	120½	6½	10	4
		M.—2 0	1/3	5.4	120	112½	7½	10½	4
6	N. S.	M.—2.0	1/5	..	123	118	5	5	1
7	W. M.	M.—2.0	1/2	..	209¾	204	5¾	7	2
		M.—2.0	1/5	..	203¾	199	4¾	8	2
8	B. J.	M.—2.0	1/31	..	164	157	7	10	2
9	H. R.	M.—2.0	2/6	..	96½	93	3½	4½	2
10	F. K.	M.—1.0	1/15	..	184	179	5	6½	2
		M.—2.0	2/6	..	166½	164	2½	2½	1

Our next step was to compare mercupurin with a mercurial diuretic having about the same mercury content per injection dose but not containing theophyllin. Salyrgan was found to meet these requirements and had the added advantage of being used extensively. In comparing the efficiency of two diuretics in man difficulties are encountered which make it hard to evaluate the results obtained. Variables are present which can be controlled only in part or not at all. The beneficial effect of diuretics seems to wear off to a variable degree in certain cases after being given over a long period.[3d, 12] They are often less effective when given close together even though the dosage be increased.[3d] On the other

hand, certain patients show an increasing response to mercurials, so that a progressively greater diuresis results. In addition, if the different diuretics are given alternately, we may have the possible delayed effect of the one given earlier. Nevertheless, in spite of these variables, if the results are all in the same direction one would be justified in attaching some significance to them.

Salyrgan is dispensed in a 10% solution containing 39.6% mercury by weight (1 cc. contains 0.0396 gm. Hg). Mercupurin is dispensed in a 13.5% solution containing 29.1% mercury by weight (1 cc. contains 0.0393 gm. Hg). Thus 1 cc. of each preparation contains approximately equivalent amounts of mercury. Each diuretic was administered, using the mercury content as the basis for dosage (except in the first 4 cases where a slightly higher dosage of salyrgan was used).

The diuretics were given alternately, allowing as nearly as possible the patient's weight to return to the initial level before the second drug was given. This was done so that approximately the same amount of retained edema was present in the body before each diuretic was given. As we have just shown, such a control is extremely important because the extent of the diuresis depends in a large part on the amount of edema present. Such a procedure entailed no hardship on the part of the patient because the patient was ready for the second diuretic at about the time it would ordinarily have been given. The cases selected for this study were those who regained weight rapidly. It is probably for this reason that the diuresis did not continue as a rule for more than 1 day, contrary to the group shown previously. In Case 12 (Table 2) the edema was so marked and the clinical condition so poor that it was not desirable to follow this rule quite so rigidly. In Case 18 (Table 3) a series of injections of salyrgan were followed by a series of mercupurin.

The results are shown in Tables 2 and 3. Of the 9 cases tabulated, in 6 mercupurin produced a greater loss of weight than salyrgan, in 2, Cases 12 and 14, the results were equivocal, and in no case did salyrgan produce a greater diuresis than mercupurin. It will be noted that mercupurin was given at times where the initial weight was below that when salyrgan was given and yet the diuresis was the same or even better. With Case 18 (Table 3) mercupurin not only produced a greater loss of weight but the interval between injections could be lengthened and still maintain the patient on a lower average weight level than when he was on salyrgan (Fig. 2).

In order to study more intimately the diuresis of the two drugs the following method was used: The patient was put under practically basal conditions. He was always allowed to regain his initial weight level before the comparison was made, otherwise the results would not be valid. Breakfast, which was essentially the same for every day the observations were made, contained very little

fluid (less than 250 cc.) and was given at 7 A.M. At 9 A.M. the patient voided and the urine was discarded. He then voided every ½ hour for 8½ hours. At 10 A.M. the diuretic was given intravenously. No fluid or food was administered during the period of observation. In the 4 cases in which this was done, it was found that the peak of the diuretic effect was between the 4th and 5th hours with both drugs, and in every case mercupurin reached a higher level and produced a greater total diuresis (Fig. 3).

TABLE 2.—COMPARISON OF MERCUPURIN (M) AND SALYRGAN (S) WHEN GIVEN ALTERNATELY.

Case No.	Case.	Diuretic cc.	Date.	Amm. chlorid, gm.	Initial wt.	Wt. first day.	Loss first day.	Max. loss.	Days required for wt. loss.
11 . . .	S. R.	M.—2.0	10/23	..	146	135	11	11	1
		S.—2.2	10/31	..	143½	136½	7	7	1
		M.—2.0	11/7	..	141	132½	8½	8½	1
		S.—2.0	11/16	..	140	133	7	7	1
		M.—2.0	11/22	..	141	131	10	10	1
		S.—2.0	11/28	..	137¾	129	8¾	8¾	1
		M.—2.0	12/4	..	139	128½	10½	10½	1
		M.—1.0	12/15	2.4	138	125	13	13	1
		S.—1.0	12/27	2.4	134	129½	4½	4½	1
12 . . .	J. K.	M.—0.9	9/3	..	134	133	1	1	1
		S.—1.0	10/18	..	131¾	130¼	1½	1½	1
		M.—0.9	10/29	..	125	119¼	5¾	5¾	1
		S.—1.0	11/7	..	123¾	120¼	3½	3½	1
		S.—2.0	11/14	..	126	117¾	8¼	8¼	1
		M.—2.0	11/21	.	120	112	8	8	1
13 . . .	S. K.	M.—0.9	10/31	..	199	195½	3½	3½	1
		S.—1.0	11/3	..	197¼	198	0	0	0
		M.—1.8	11/7	..	200¼	191	9¼	9¼	1
		S.—2.0	11/12	..	195	192½	2½	2½	1
		M.—2.0	11/15	..	191	183½	7½	7½	1
		M.—2.0	11/20	1.8	183½	178	5½	5½	1
14 . . .	E. D.	S.—2.2	11/6	..	147	139	7½	7½	1
		M.—2.0	11/13	..	143½	135	8½	8½	1
15 . . .	J. B.	S.—2.0	12/18	..	154	154½	0	0	0
		M.—2.0	12/29	..	151	142	9	9	1
		S.—2.0	1/4	..	150	147½	2½	2½	1
16 . . .	H. G.	M.—2.0	12/29	..	154	144	10	10	2
		S.—2.0	1/8	..	148½	141	7½	8½	2
		M.—2.0	1/26	..	143	133	10	10	1
17 . . .	F. G.	M.—1.0	1/15	..	146	146	0	0	0
		M.—2.0	1/18	..	146	146½	0	0	0
		S.—2.0	1/21	..	158	159	0	0	0
		M.—2.0	1/25	5.4	158	158½	0	0	0

Although these experiments suggested that the presence of theophyllin in a mercurial diuretic would enhance somewhat the

effectiveness of the diuretic, still the experiment was not ideal. Although salyrgan and mercupurin contain approximately the same amount of mercury per dose, still the organic portion of the molecule differs considerably. Therefore, it is possible that this variation in chemical structure rather than the presence of theophyllin might be responsible for the difference in diuretic effectiveness. For that reason a quantity of the theophyllin-free mercurial salt of mercupurin was obtained and put into solution so that the mercury content per dose would be the same as that of mercupurin. Four cases were studied and results are given in Table 4.

TABLE 3.—SUBSTITUTION OF MERCUPURIN (M) FOR SALYRGAN (S) AND VICE VERSA.

Case No.	Case.	Diuretic, cc.	Date.	Amm. chlorid, gm.	Initial wt.	Wt. first day.	Loss first day.	Max. loss.	Days required for wt. loss.
18 . . .	E. B.	S.—1.0	11/18	..	189	192½	0	0	0
		S.—2.0	11/22	..	190½	184	6½	6½	1
		S.—2.0	11/24	3.6	184	180	4	4	1
		S.—2.0	11/27	..	186	182	4	4	1
		S.—2.0	11/30	..	185	180	5	5	1
		M.—2.0*	12/2	..	182½	180	2½	4	2
		M.—2.0	12/6	..	183	176	7	7	1
		M.—2.0	12/11	..	182	177	5	5	1
		M.—2.0	12/15	..	181½	176	5½	5½	1
		M.—2.0	12/19	..	182½	176	6½	6½	1
		M.—2.0	12/24	..	185	177	8	8	1
		M.—2.0	12/28	..	184	176	8	8	1
19 . . .	F. S.	M.—2.0	2/27	..	118½	114	4½	4½	1
		M.—2.0	3/9	..	118	113	5	5	1
		M.—2.0	3/20	..	117½	113	4½	4½	1
		S.—2.0	4/4	..	118½	116	2½	2½	1
		S.—2.0	4/16	..	119½	117½	2	2	1

* Intramuscular injection.

In 2 cases (Nos. 15 and 20) a greater weight loss occurred with mercupurin than with the theophyllin-free salt. In the 2 others, Cases 18 and 19, the weight loss was about the same for each. This may be due to the fact that the small amount of edema initially present in these 2 patients needed only a small dose of a diuretic to bring the weight down to a basal level, and that the doses given here were therefore in excess of that required. In order to study the difference more closely in these 2 cases, half-hour observations of urinary output, as described above for the comparison of salyrgan and mercupurin, were done. In both cases there was a greater diuresis produced by mercupurin than its salt free of theophyllin. A comparison was also made with salyrgan and it was found that salyrgan and the mercurial salt free of theophyllin gave practically the same results (Fig. 4). These experiments further support the view that it is the presence of theophyllin in the mercupurin which accounts for the greater diuresis.

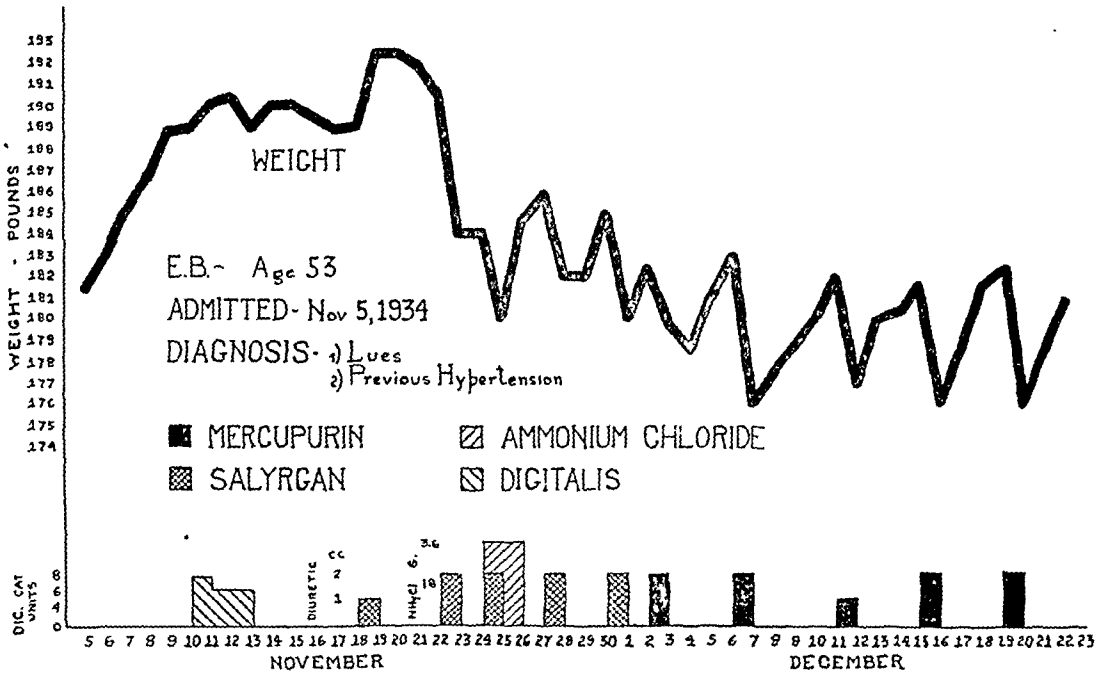


FIG. 2.—Showing greater loss of weight and maintenance on a lower average weight level when mercupurin was substituted for salyrgan (Case 18, Table 3).

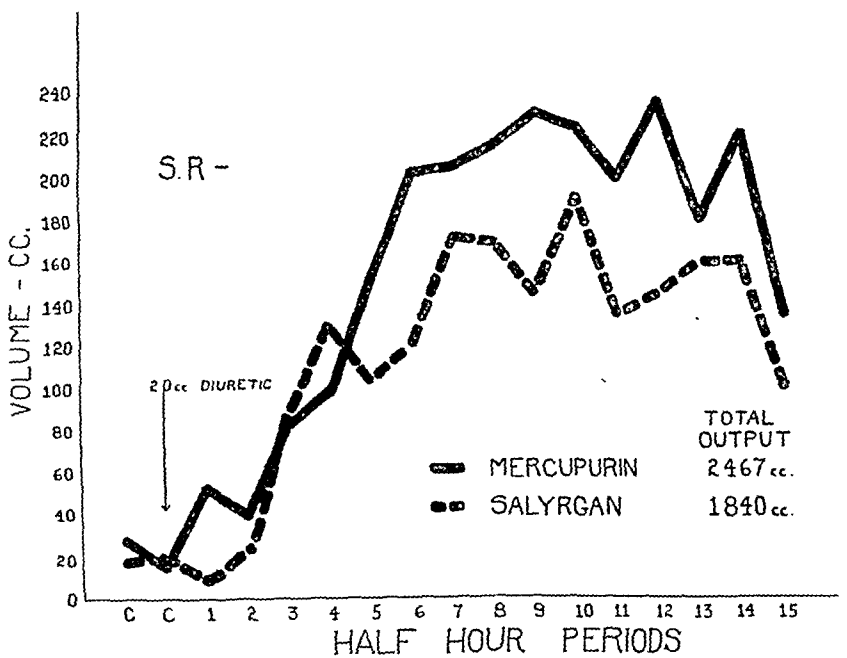


FIG. 3.—Half-hour observations of the urinary output following administration of mercupurin and salyrgan. Patient was allowed to regain initial weight before either diuretic was given (Case 11).

TABLE 4. SHOWING RÔLE PLAYED BY THEOPHYLLIN FRACTION OF MERCUPURIN BY COMPARING MERCUPURIN (M) WITH THE MERCURIAL SALT CONTAINED IN MERCUPURIN FREE OF THEOPHYLLIN (M–T).

Case No.	Case.	Diuretic, cc.	Date.	Amm. chlorid, gm.	Initial wt.	Wt. first day.	Loss first day.	Max. loss.	Days required for wt. loss.
15 . . .	J. B.	M.—2.0	12/29	..	151	142	9	9	1
		M-T—2.0	1/15	..	145½	140	5½	5½	1
		M.—2.0	1/21	..	142	138	4	4	1
		M.—2.0	1/24	..	139	135½	4½	4½	1
		M.—2.0	2/2	3.6	135	130	5	6	2
		M.—2.0	2/5	3.6	129½	121	8½	8½	1
		M.—2.0	2/11	3.6	125	118	7	7	1
		M-T—2.0	2/21	3.6	122½	120½	2	2	1
		M.—2.0	2/26	3.6	126¾	121	5¾	5¾	1
		M-T—2.0	2/28	3.6	125½	121¾	3¾	3¾	1
		M.—2.0	3/5	3.6	128	124	4	4	1
		M-T—2.0	3/7	3.6	127½	123	4½	4½	1
		M.—2.0	3/12	3.6	129	121	8	8	1
18 . . .	E. B.	M.—2.0	12/28	..	184	176	8	8	1
		M-T—2.0	1/22	..	184	177	7	7	1
20 . . .	P. S.	M.—2.0	2/4	..	172½	166	6½	6½	1
		M.—2.0	2/9	..	163	161	2	8	3
		M-T—2.0	2/14	..	156	156	0	0	0
		M-T—2.0	2/19	5.4	150¼	149	1¼	5¼	3
		M.—2.0	2/22	5.4	145	142	3	8½	2
19 . . .	F. S.	M.—2.0	2/27	..	118½	114	4½	4½	1
		M-T—2.0	3/5	..	116½	113	3½	3½	1
		M.—2.0	3/9	..	118	113	5	5	1
		M-T—2.0	3/14	..	117½	113	4½	4½	1
		M.—2.0	3/20	..	117½	113	4½	4½	1
		M-T—2.0	3/28	..	117½	113	4½	4½	1

In no case was a slough or venous thrombosis produced with 94 intravenous injections of mercupurin, but out of 27 intravenous injections of salyrgan 4 cases developed a thrombosis or slough. The local reactions of both these drugs and the part played by theophyllin will be discussed fully in a subsequent paper.[13]

Although frequent and careful microscopic urine examinations were made throughout, no evidence of damage to the kidney was noted in any case with any of the drugs used. Even in the patient having glomerulonephritis (Case 16), where a mercurial diuretic had to be given because nothing else was effective, no evidence of increased kidney damage due to the mercurials could be detected from a study of the urinary sediment.

Discussion. Organic preparations of mercury in a non-ionizable form have replaced the use of calomel in the treatment of edema. It has been suggested by v. Issekutz and v. Vegh,[4] and later by Fourneau and Melville,[14] that the chemical structure of the various

preparations is an important factor in determining diuretic efficiency and toxicity. Thus, the latter conclude that "mercurial toxicity is not in direct relation to either the quantity *per se* of mercury injected or to the general chemical reactivity of the substance as shown by the action of certain chemical reagents, but rather dependent primarily upon the direct chemical linkage of the metal," while "structural changes in chemical constitution might lead to variation in diuretic activity." It will be recalled that the theophyllin-free mercurial salt of mercupurin differs in its structural formula from that of salyrgan and theoretically should therefore differ in its toxicity and diuretic effectiveness. The evidence submitted by v. Issekutz and v. Vegh[4] indicates that salyrgan is more toxic than the theophyllin-free mercurial salt of mercupurin, but neither they, in their animal experiments, nor we, in our work in man, were able to detect any measurable differences in the diuretic effectiveness of the two drugs.

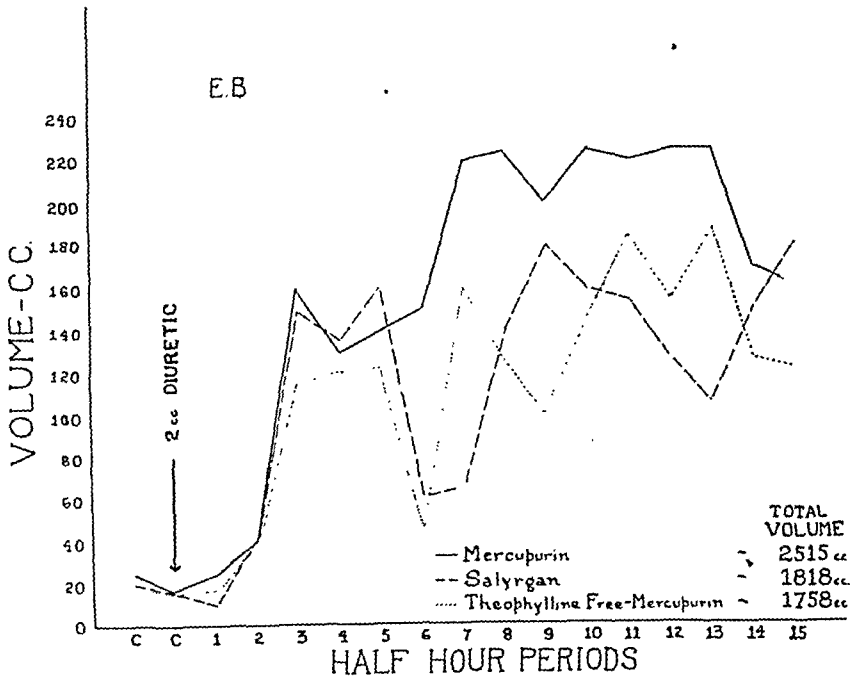


FIG. 4.—Half-hour observations comparing mercupurin, salyrgan and the theophyllin-free mercurial salt contained in mercupurin. Patient was allowed to regain initial weight before each diuretic was given (Case 18).

The question of the mechanism of the diuresis resulting with xanthin and mercurial preparations, although still open to dispute, was markedly clarified with the use of Rehberg's[15] method for measuring glomerular filtration and tubular reabsorption. Evidence at the moment indicates that both the xanthins and mercurials have their action directly upon the kidney, the former increasing

glomerular filtration and the latter decreasing tubular reabsorption. The literature on this subject has been recently reviewed by Schmitz[16a] and Binger and Keith.[16b] If the mechanism of diuresis is such that both types of diuretics have different sites of action in the kidney, it is evident then that upon purely theoretical grounds a combination of both would possess possible advantages. The results of v. Issekutz and v. Vegh,[4] who were the first to use a combination of both diuretics, have already been discussed. Recently Herrman[17] and his coworkers have likewise found clinically that, when the diuretics were given together or alternately, a better clinical result was obtained.

From our results it is also seen that theophyllin plays a part when combined with a mercurial salt in the removal of edema fluid. This is in accord with the results of Crawford and McDaniel[7] in their comparison of mercupurin and salyrgan and the experimental work of Fulton and Bryan.[8]

Conclusions. 1. Mercupurin is an effective and safe diuretic.

2. The diuretic effect of mercupurin is greater than that of a mercurial diuretic not containing theophyllin.

3. The superiority of mercupurin is chiefly if not entirely due to the presence of theophyllin.

4. No local reaction from intravenous administration of mercupurin was noted in 94 injections.

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ON THE DIFFERENTIATION OF COLORED CEREBROSPINAL FLUIDS.

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In this communication we wish to report upon studies of colored spinal fluids; to try to define more exactly their mode of production and to suggest the routine use of the benzidin test in their etiologic differentiation.

Froin,[1] in 1903, first directed attention to the "syndrome de coagulation massive et de xanthochromia" which now bears his name. Nonne,[2] some 5 years later, described a marked increase in protein, but with no pleocytosis or xanthochromia in 3 cases of cord tumor. Hanes,[3] in 1916, correlated the findings of Froin and Nonne by pointing out that the Nonne syndrome represents the earliest spinal fluid change in cord compression, whereas the Froin syndrome is the result of long-standing cord compression which produces a cul-de-sac distal or caudad to the lesion. "Any pathologic alteration of the vertebræ, dura mater or pia arachnoid which leads to partial or complete obliteration of the pia arachnoid space and the formation of a cul-de-sac is capable of producing the syndrome of xanthochromia with excess protein and massive coagulation. If the pathologic change is associated with inflammation of

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the meninges there will be a leukocytosis of the fluid, but when the compression is due to non-inflammatory growths no pleocytosis is present." Ayer,[4] in 1919, produced xanthochromia with an increase of protein without pleocytosis in cats by the epidural injection of molten paraffin.

Colored spinal fluids (1) may be produced by hemorrhage into the subarachnoid space, (2) by spinal cord compression, (3) by severe inflammatory reactions, (4) by carotinemia and (5) are found in the xanthochromia of the newborn. Obviously it would be of great aid if some simple test could be used which would separate yellow fluids due to compression on the one hand, from tingeing of the fluid from hemoglobin or its derivatives. During the past 3 years the benzidin test as modified by Schlessinger and Holst[5] has been used routinely in the medical clinic of Duke Hospital upon all spinal fluids. Devine and Robinson, of this clinic, by a carefully controlled series of studies (unpublished) were able to show that the benzidin test for hemoglobin in the cerebrospinal fluid is positive in dilutions up to 1 in 50,000 (or about 100 red cells per cc.), but is negative in dilutions of 1 in 100,000 (or 50 cells per cc.). In a series of 100 fluids obtained from routine punctures they found that 12 (8%) gave a positive benzidin test, and all of these contained more than 100 cells per cc. After centrifuging such fluids the supernatant fluid did not give a positive benzidin test.

The conditions are quite otherwise in cerebrospinal fluids discolored by subarachnoid hemorrhage. Here, except in very early bleedings, which cause no confusion, the supernatant fluid after centrifuging gives a strongly positive benzidin reaction. We have been able to follow the cerebrospinal fluid in 1 case of subarachnoid hemorrhage until all tingeing had disappeared, but this perfectly clear untinged fluid still gave a positive benzidin reaction.

The literature contains very few data on the benzidin reaction of the yellow fluids found in the cord compression syndrome. This problem seemed peculiarly suited to experimental study. We have devised the following method by means of which a slowly developing compression of the spinal cord in dogs can be produced. The laminæ of the third and fifth thoracic vertebræ are resected, leaving the fourth lamina in place. If now a small collodion bag filled with a concentrated suspension of gum acacia is placed beneath the fourth lamina extradurally, and the wound closed, the collodion bag slowly distends and compresses the cord. Bags of various sizes were used, containing from 0.25 to 0.5 cc. of gum acacia and compressions of varying severity could thereby be accurately produced. From our 14 protocols we have selected 4 as typical.

Protocols. *Dog 4.*—A collodion sac filled with a solution of acacia was inserted epidurally under the fourth thoracic vertebra. The dog walked for 2 days without motor impairment and then began to manifest increas-

ing spasticity of the lower extremities which amounted to a paraplegia on the 8th day. On this day the cerebrospinal fluid below the block was clear yellow and [illegible]nding, reacted negatively to the benzidin test, gave a 3+ [illegible] and contained 8 leukocytes per c.mm., no erythrocytes. The dog was sacrified and autopsied on the 14th day and the fluid at this time was yellow, gave a negative benzidin reaction, a 3+ Pandy, contained 18 leukocytes and no erythrocytes. The cord was found compressed by the collodion bag and the veins of the spinal canal and dura were markedly dilated below the block and slightly dilated for a few centimeters above the block.

Dog 7.—A collodion bag containing a concentrated solution of glucose was inserted epidurally in this case and the dog was unable to walk after operation. Prior to autopsy on the 4th day, however, slight return of function was noted. A lumbar puncture was done about 18 hours after operation and the fluid was clear, colorless, contained 2 leukocytes and gave a negative benzidin and Pandy reaction. On the 4th day the animal was sacrificed and autopsied. The collodion bag was found to have ruptured and the dura was adherent at the level of the block. There was only slight venous engorgement below the block. The cerebrospinal fluid was yellow, contained 10 leukocytes and gave a negative benzidin reaction and a 3+ Pandy.

Dog 8.—One day after operation (collodion and acacia bag) this dog began to show weakness of the hind legs in walking, which progressed to a paraplegia by the 3d day and continued throughout the course of the experiment. On the 3d day the cerebrospinal fluid below the block was removed. It was yellow, gave a negative benzidin reaction, a 3+ Pandy, contained 6 leukocytes and 82 erythrocytes. A lumbar puncture on the 10th was contaminated with blood and it was noted that the last drops did not appear bloody. This fluid contained 18 leukocytes, 576 erythrocytes, gave a strongly positive benzidin reaction and a 3+ Pandy. After centrifuging at high speed, the supernatant fluid was yellow, contained no cells and gave a 3+ Pandy reaction and a negative benzidin. At autopsy on the 10th day the cord was found compressed by the collodion bag and the veins of the spinal canal and dura were markedly engorged below the block and obliterated at the level of the block with a slight engorgement for 2 or 3 cm. above the site of compression.

Dog 2.—This dog began to manifest some weakness of the hind legs on the day after operation (collodion and acacia bag) which progressively became more marked, but he was able to move his legs at the time of his sacrifice on the 3d day. On this day an autopsy was performed and the cerebrospinal fluid below the block was yellow, contained 6 leukocytes, no erythrocytes, gave a negative benzidin reaction and a 3+ Pandy. The cord was found only slightly compressed. The veins at this level, however, were obliterated. They were engorged below the block and were slightly more prominent than normal for a few centimeters above the level of compression.

Dog 14.—In this case a tape, about 1 cm. in width, was tied snugly about the cord epidurally, and immediately after the animal regained consciousness a paraplegia was evident. The animal was left with this paraplegia in extension for 5 days and then autopsied. The cerebrospinal fluid below the block was yellow, clear and contained 4 leukocytes, no erythrocytes, gave a 3+ Pandy and a negative benzidin response. The tape constricted the spinal cord to a rather marked degree and also pressed against the anterior longitudinal veins of the canal and obliterated them at this level; but they were markedly engorged below the block and for a few centimeters above the block were more than normally prominent. The veins of the dura below the block were engorged.

In every case a routine cisterna puncture was done at autopsy and the cerebrospinal fluid removed was uniformly normal.

Comment. The severity of the symptoms of cord compression was directly proportional to the size attained by the collodion bag and to the duration of the compression. As a rule, the animal was able to walk quite normally for 2 or 3 days following the operation, but a progressive weakness of the legs then developed which, on the fourth day, culminated in paraplegia in extension.

Cerebrospinal fluids removed by lumbar puncture within the first 24 hours were quite normal, and fluids removed from the cisterna magna were always normal regardless of the severity or duration of the cord compression. After the first day the changes in the cerebrospinal fluid below the block were remarkably constant. There was at first a marked increase in protein, which in prolonged blocks resulted in spontaneous massive coagulation of the fluid removed. Such fluids showed a canary yellow color, but no pleocytosis. *The benzidin reaction was uniformly negative on all fluids.* We feel that we can state positively that the cerebrospinal fluid in the pure syndrome of spinal cord compression does not give a benzidin reaction.

At *autopsy* identical findings were observed in all animals, consisting of compression of the cord by the distended bag with obliteration of the subarachnoid space and the formation of a cul-de-sac below the block. For about 3 cm. above the area of compression and 7 cm. below the venules of the leptomeninges were greatly engorged. Lying extradurally there are 2 longitudinal veins in the anterior portion of the spinal canal which anastomose with radicles from each segment of the cord, and with veins which run along the vertebral column outside the canal. These veins were found to be compressed at the region of the block and engorged for a few centimeters above and below the block, in which latter position they were especially prominent, being about 3 times their normal size. Microscopic studies of the spinal cords showed no inflammatory changes.

Discussion. The possibility of distinguishing between xanthochromia, whether due to hemorrhage, to inflammation or to cord compression, has been denied by certain observers.[6] Hanes,[3] in 1916, in his discussion of a case of spinal block with yellow fluid of high-protein content, pointed out that the benzidin reaction was negative and that the veins below the block were greatly engorged. He suggested that such spinal fluid findings were due purely to venous stasis with transudation. Our results support this conclusion. We believe that the benzidin reaction offers a simple and positive means of differentiation between spinal block without inflammation on the one hand, and hemorrhagic xanthochromia on the other. The use of the designation "erythrochromia" for tingeing of the fluid due to hemorrhage or inflammatory diapedesis,

and the restriction of the term xanthochromia to the yellow fluid, rich in protein, of the pure Nonne-Froin pressure syndrome, seems justifiable in the light of the experiments here reported.

Summary. 1. The benzidin reaction is positive in cerebrospinal fluid containing a hemoglobin dilution of 1 to 50,000 (100 erythrocytes per c.mm.), but not to a dilution of 1 in 100,000 (50 erythrocytes per c.mm.).

2. The benzidin reaction on the supernatant fluid after centrifuging at high speed is of value in differentiating hemorrhage into the cerebrospinal fluid at the time of puncture from subarachnoid hemorrhage.

3. An extramedullary tumor compressing the spinal cord in its growth has been reproduced experimentally in dogs with a resulting Nonne-Froin syndrome in the cerebrospinal fluid below the level of the compression.

4. The yellow spinal fluid of cord compression gives a negative benzidin reaction.

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EARLY PULMONARY TUBERCULOSIS AND ITS DIAGNOSIS.

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The Problem. Though the importance of early diagnosis has been heralded for years, pulmonary tuberculosis is usually not discovered in its minimal stage. Upward of 80% of patients on admission to sanatoria are either in a moderately or far advanced stage of the disease. Treatment then usually requires a long period of time, often presents many difficulties, and the prognosis is only mildly encouraging, viewed after 5, 10 and 15 years. Whitney[1] reports that of 37,665 cases of frank pulmonary tuberculosis reported by 274 institutions (U. S.) in 1931, 5939 (16%) were admitted in the minimal stage, 11,057 (30%) in the moderately advanced and

19,669 (54%) in the far advanced stage. Compared to the earlier figures (1926) of Drolet,[2] the percentage admitted in the minimal stage, 16%, is the same, but in 1931 the percentage of far advanced is higher, being 54% as compared with 50% in 1926.

Watt[3] of England, successfully tracing 603 of 677 cases 5 years after their discharge in 1925 from the King George V Sanatorium, found that of 149 early cases, 21.5% were dead, 64.5% alive and fit for work, and 14% alive but not fit for work. Of 385 moderately advanced cases, 63.5% were dead, 24.5% alive and fit for work, and 12% alive and not fit for work. Of 69 far advanced cases, 91% were dead, 4.5% alive and fit for work, and 4.5% alive but not fit for work. Today with better methods of treatment the mortality rate would undoubtedly be less but still substantial. The figures of the early cases after 5 years offer a striking contrast to those of the moderately and far advanced cases. The report of the Trudeau Sanatorium[4] also emphasizes the necessity of early diagnosis. After 15 years only 10% of the minimal are dead, compared to 27% of the moderately advanced and 72% of the far advanced cases.

TABLE 1.—CONDITION OF DISCHARGED PATIENTS (TRUDEAU SANATORIUM) 5, 10 AND 15 YEARS AFTER DISCHARGE.

Classification on admission.	Dead of tbc. first 5 yrs. No.	Dead of tbc. first 5 yrs. %	Dead of tbc. second 5 yrs. No.	Dead of tbc. second 5 yrs. %	Dead of tbc. third 5 yrs. No.	Dead of tbc. third 5 yrs. %
Minimal, 627 (20%)	21	3.3	24	3.1	17	3.6
					Total, 15 yrs., 62	10.0
Moderately advanced, 2033 (65%)	242	11.9	262	10.0	131	5.5
					Total, 15 yrs., 635	27.4
Far advanced, 449 (14%) . .	196	43.6	83	18.0	104	10.6
					Total, 15 yrs., 383	72.2

TABLE 2.—PROGNOSIS OF 37,665 CASES OF PULMONARY TUBERCULOSIS ADMITTED TO 247 U. S. INSTITUTIONS 1931, ACCORDING TO THE TRUDEAU SANATORIUM EXPERIENCE.

Classification on admission.	Dead of tbc. first 5 yrs. No.	Dead of tbc. first 5 yrs. %	Dead of tbc. second 5 yrs. No.	Dead of tbc. second 5 yrs. %	Dead of tbc. third 5 yrs. No.	Dead of tbc. third 5 yrs. %
Minimal, 5939 (16%)	196	3.3	184	3.1	214	3.6
					Total, 15 yrs., 594	10.0
Moderately advanced, 11,057 (30%)	1,345	11.9	1,130	10.0	621	5.5
					Total, 15 yrs., 3,096	27.4
Far advanced, 19,669 (54%) . .	8,577	43.6	3,540	18.0	2,084	10.6
					Total, 15 yrs., 14,201	72.2

The experience of patients in the minimal, moderately advanced and far advanced groups 5, 10 and 15 years after discharge from the Trudeau Sanatorium is shown in Table 1. Table 2 represents

the prognosis of 37,665 cases admitted to 274 United States Sanatoria in 1931 based on the Trudeau experience. Why only 16% are admitted in the minimal and 54% in the far advanced stage with prognosis bad, requires an explanation. The explanation, as will be shown, lies in the fact that pulmonary tuberculosis in its minimal stage is without symptoms sufficient to bring the patient to the physician, and without physical signs in most instances by which a diagnosis could be made if the patient did present himself. The discovery of early tuberculosis is dependent on the roentgenogram and fluoroscopic examination of those infected as determined by the properly administered Mantoux tuberculin test.

Gaspard-Laurent Bayle rightfully wrote over a century ago: "Many physicians seem to have confused phthisis with its characteristic signs, and as emaciation and the hectic fever are two of the ordinary symptoms of phthisis, it seems absurd to them to consider an individual as suffering from phthisis, in whom no fever nor emaciation can be discovered. This manner of considering phthisis is just as ridiculous as that of the naturalist, who seeing a young oak tree, would refuse absolutely to give it this name because it did not yet show all its generic and specific characteristics. Moreover, the oak which has just grown out of the ground, although it is a very feeble plant, is none the less a tree whose trunk will acquire a great deal of strength. It is the same with phthisis: in the beginning it seems scarcely a slight indisposition: in its last stages it strikes down the strongest man, it devours, consumes and reduces to a skeleton those whose plumpness, freshness and health appeared unalterable. Nevertheless, it would be unreasonable to refuse to admit that it is always the same disease, and to maintain this opinion and insist that in its earliest stages it did not show all the symptoms which characterise it today.

". . . But today our knowledge is too advanced to fail to diagnose phthisis in the first stages of this disease, although frequently there has been no perceptible loss of weight and not the slightest trace of pus in the expectoration. . . . It would be hardly reasonable to wish to wait before diagnosing pulmonary phthisis until it had arrived at its last stage which is the time when its pathognomonic symptoms are well marked. Is it not then undebatable that a physician should seek to know a disease from its beginning, through all the stages of its development, and in all its forms, just as the gardner distinguishes the plants which he cultivates through all the stages of their growth, and as an entomologist recognizes an insect in all its metamorphoses?"

Today we are learning more of the disease in its early stage, and have already found the important fact that many times it produces less than the slight indisposition spoken of by Bayle—that in most instances it occurs without producing symptoms or physical signs.

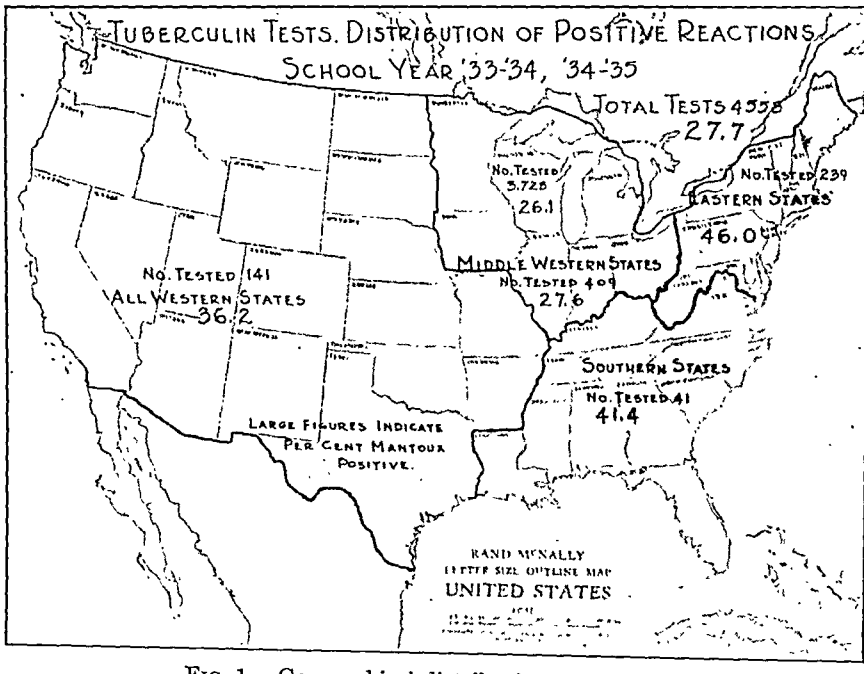


FIG. 1.—Geographical distribution of infection.

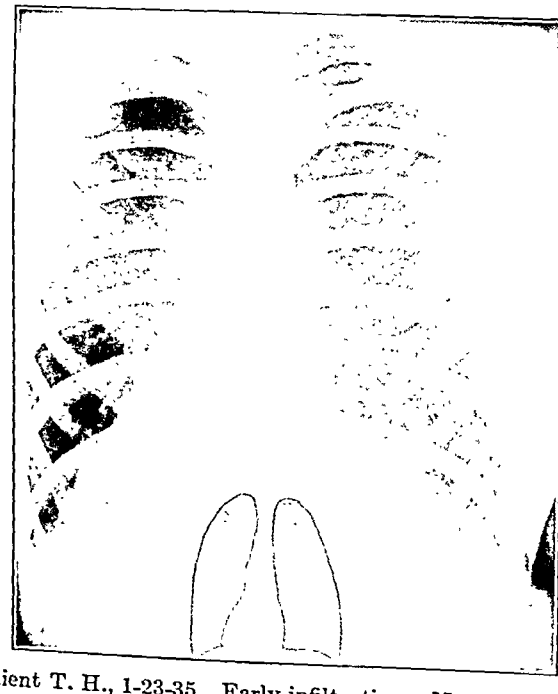


FIG. 3.—Patient T. H., 1-23-35. Early infiltration. No symptoms or physical signs. Laboratory studies negative.

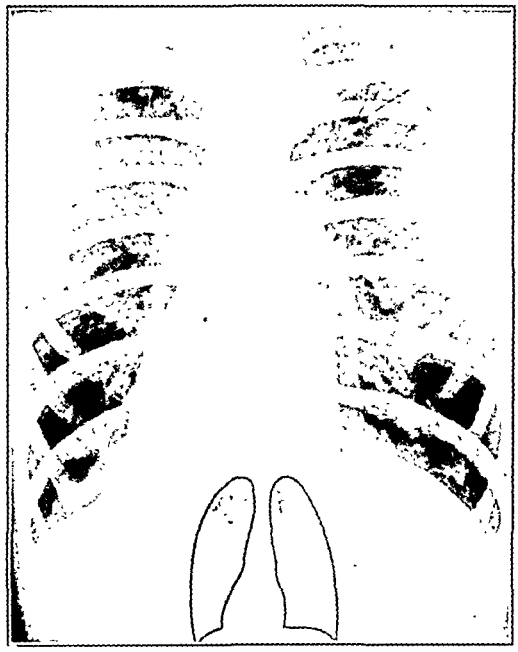


FIG. 4.—Patient T. H., 6-1-35. Spread of lesions without symptoms or physical signs. Patient has gained 8 pounds in weight. Laboratory studies indicative of spread.

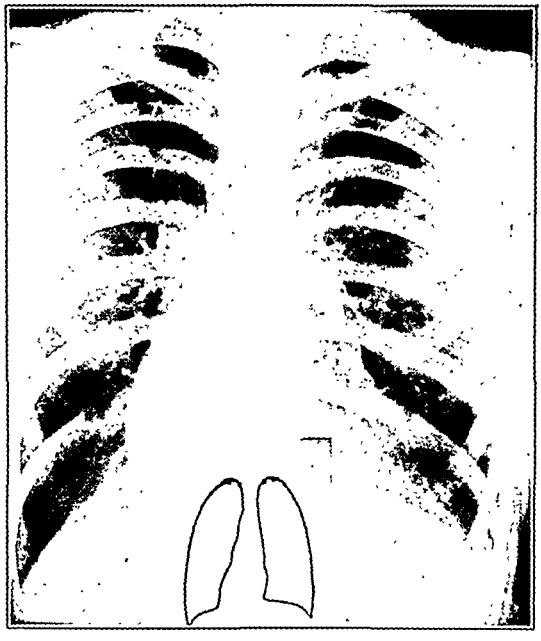


FIG. 6.—Case 80551, 2-10-35. Small infiltration at extreme apices. Negative studies.

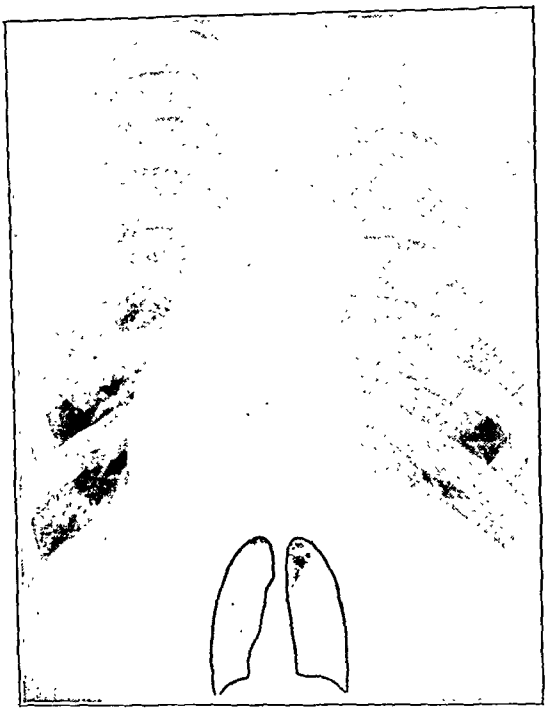


FIG. 7.—Case 80551. Lesion 11 months later; discovered by fluoroscopic examination. Weight gain, 11 pounds. Leucocytosis. No other positive studies.

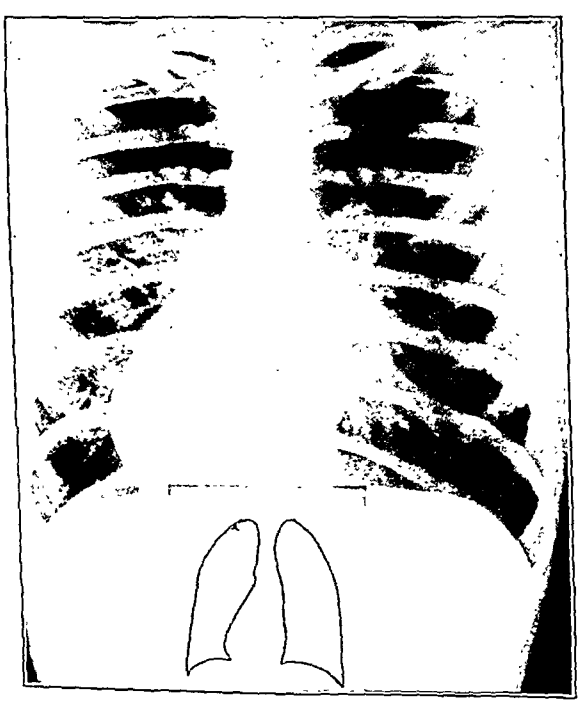


FIG. 9.—Case 73344. Small infiltration discovered by fluoroscopic examination.

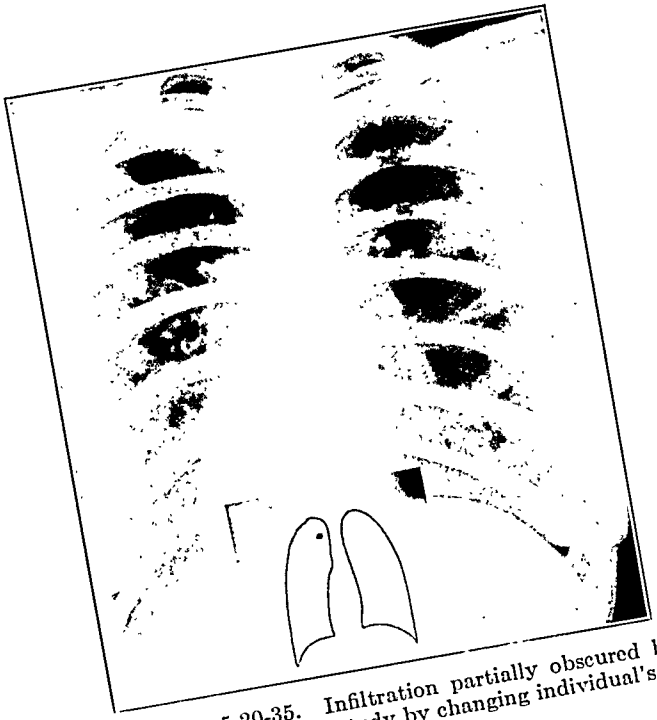


FIG. 10.—Case 69634; 5-20-35. Infiltration partially obscured by bony framework, clearly visible by fluoroscopic study by changing individual's position.

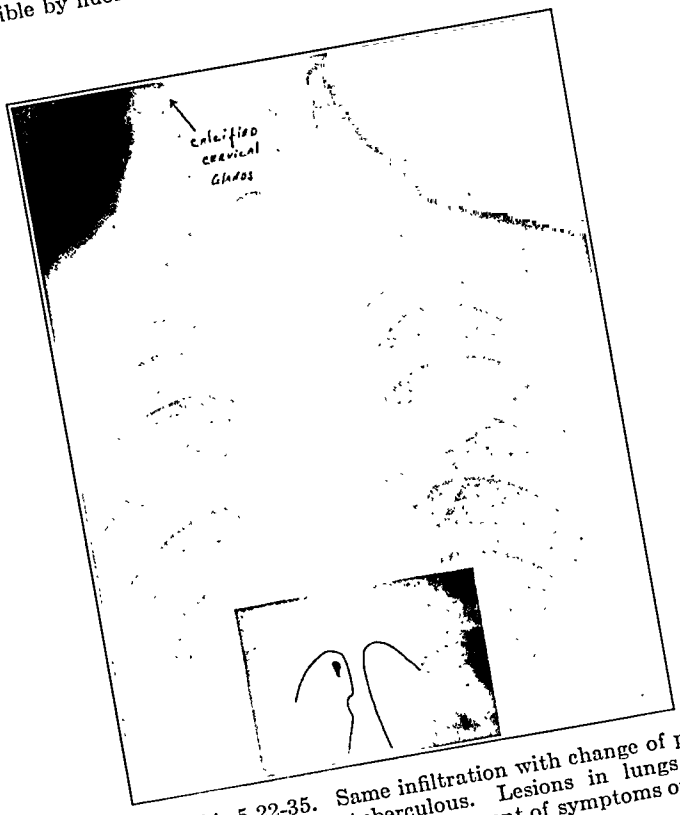


FIG. 11.—Case 69634; 5-22-35. Same infiltration with change of position. Note calcified cervical nodes. Tonsils tuberculous. Lesions in lungs, 12-10-35, has spread to six clavicular regions without development of symptoms or physical signs.

The Program. A case-finding study was instituted in the fall of 1933 on all the newly enrolled students. With the routine physical examination, all students are given the Mantoux test. At the first test either 0.1 mg. of the Saranac Laboratory old tuberculin (O.T.) or 0.00002 mg. of the Purified Protein Derivative (P.P.D.) of Seibert and Long is given. The site of the injection is observed at the end of 48 hours and if no reaction has occurred, the procedure is repeated, using 1 mg. O.T. or 0.005 mg. P.P.D. Those showing positive reactions are further studied by means of the roentgenogram. Infiltrations are thus discovered that require further immediate study which is done in the Student Infirmary. The status of the lesion having been determined, the patient is either advised to withdraw from school for treatment or given instructions to report for examination at regular intervals. Those having suspicious shadows are examined by means of the fluoroscope and Roentgen ray films at intervals of from 4 to 12 weeks, depending upon the degree of suspicion attached to the lesion. Regardless of the fact that the first film may be negative, the tuberculin-positive student receives a fluoroscopic examination every 6 to 12 months while he is attending school. Should the fluoroscopic examination reveal any suspicion of trouble, another roentgenogram is requested. In an individual of heavy proportions, the fluoroscope has its limitations, and is not relied upon to exclude an early infiltration. In those, however, of moderate or light build it makes possible, in our opinion, the discovery of all significant infiltrations to a degree which closely approximates the roentgenogram.

Tuberculin Tests. Of a total of 5316 individuals tested with a dose of at least 1 mg. O.T. or 0.005 mg. P.P.D., 1490 (28%) have shown positive reactions.

The distribution of infection among students from different sections of the country is shown in Figure 1.

To determine the rate of increase of infection, a group of students entering the University in the fall of 1933 and having negative reactions at that time was again tested 18 months later. Of the 485 originally negative students tested, 45 (9.3%) had become infected.

The opportunity was also presented to test a group of 15 sorority girls who had unfortunately lived for 3 months with a senior girl who had entered the university prior to the institution of the program and who subsequently was found to have far advanced tuberculosis. Examination of her sputum showed many tubercle bacilli. Of the 15 tuberculin tested, 11 had formerly been negative. Eight had been tested in the fall of 1933 and 2 in the fall of 1934. One received a test in high school in 1932 which was reported negative. Of the 11 known to have been negative, all (100%) showed a positive reaction in March, 1935. Of the 4 having no previous test, 3 (75%) were positive. The one individual show-

ing a negative test stated that she had lived in the house for only 2 weeks, and this short contact probably explains her escape from infection. Of the 15 tested, 14 (93.3%) showed a positive reaction. Of the 11 known to have been infected, one has developed a progressive lesion (November, 1935) in the left subclavicular region.

Cases Without Symptoms or Physical Signs. Study of the early cases discovered, a few of which are presented, indicates that the progressive pathologic process occurs without the production of symptoms or physical signs. Development of symptom and physical signs indicates in most instances that the disease is no longer in the minimal stage. One individual developed, from a small rather hard appearing right subclavicular infiltration which had shown no change during 11 months observation, a 2.5 cm. by 1.5 cm. cavity between January 22, 1935, and March 4, 1935, a period of 40 days. His only symptom was slight fatigue, and he was already

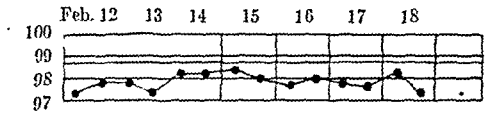
FIG. 2.—CASE NO. 79480. T.H. OCTOBER, 1933.

History: Home, city. Scarlet fever, age 10. Always healthy. Father died of appendicitis; mother living and well; brothers, 1 living and well; sisters, 0. Mantoux, ++.

Symptoms: None.

Physical Examination: Well-developed and nourished, healthy appearing boy, aged 20. Chest examination: essentially negative in October, 1933, January, 1934 and June, 1934. Bl. pr., 114/74, ht., 5′8″, wt., 120, September, 1933. Wt., 130, January, 1934. Wt., 138, June, 1934.

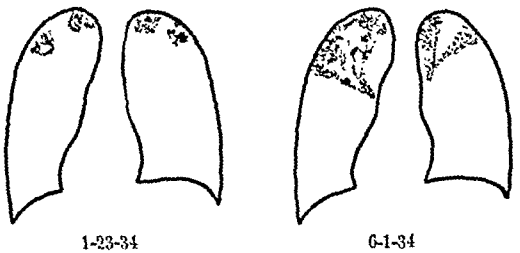
Temperature:



Normal on occasion of three office calls in June. Family physician on a 4-hr. check has never observed a fever, June–July, 1934.

Laboratory: Blood sedimentation index: 3 mm. on January 9, 1934; 4 mm. on March 16, 1934; 12.5 mm. on June 1, 1934. Blood count: leuk., 13,450; polys., 74%; lymph., 26%. No sputum examination. No examination of gastric content.

Roentgenograms:



Treatment: Sanatorium care advised.

Subsequent course: Resting at home. Family physician states, January, 1935, that patient has on no occasion had a fever. No Roentgen ray has been taken to show progress.

April 26, 1935: Roentgenologist reports clearing of infiltrations. Patient continues to be free of symptoms.

in the moderately advanced stage of the disease. Examination of the morning gastric contents of his stomach showed the presence of tubercle bacilli. As concerns symptoms with progressive minimal infiltrations, the individual will occasionally admit slight fatigue. The earliest and most suggestive physical finding, if one be present, is decreased excursion, usually in the subclavicular region, on the affected side.

Case 79480 represents a progressive lesion without the production of symptoms or physical signs. Note the gain in weight of 18

pounds. The blood sedimentation index done on the date of the latest Roentgen ray heralded the spread of the lesion. A more recent report (April, 1935) indicates that the infiltration has shown marked clearing on a regimen of rest at home. On no occasion during his treatment has a fever been found to be present.

FIG. 5.—CASE NO. 80551. J. F. FEBRUARY, 1934.

History: Home, city. Always well. No childhood or other diseases. Mother dead, rheumatic fever; father living and well; brothers, 2 living and well; sisters, 1 living and well. Mantoux, +, September, 1933.

Symptoms: None.

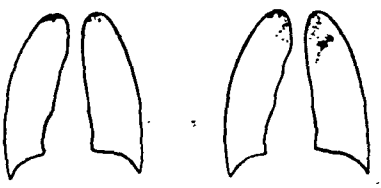
Physical examination: Nothing pertinent. Chest examination: Negative, September, 1933, February, 1934, February, 1935. Ht., 70″; wt., 125, September, 1933; wt., 138, February, 1935.

Temperature: Week of February 27, 1934, normal. Week of February 2, 1935, normal.

Laboratory: Blood sedimentation: 3 mm., February, 1934, and 3 mm., February, 1935. Leukocyte count, 12,700; polys., 73%; lymph., 25%; L.L., 2%. No sputum available for examination. Gastric aspiration not done.

Fluoroscopic examination: January 14, 1935: Feels well; no symptoms referable to chest; half-dollar-sized infiltration in right subclavicular region; stereo of chest requested.

Roentgenograms:



2-10-34 1-14-35 2-21-35

Treatment: Entered sanatorium in February, 1935.

Subsequent course:

FIG. 8.—CASE NO. 79831. A. S. DECEMBER, 1933.

History: Measles, mumps and chickenpox in childhood. Always well. No known tuberculosis contacts. Father living, not well, arthritis; mother living and well; brothers, 0; sisters, 1 living and well. Mantoux, ++; 0.1 mg., September, 1933.

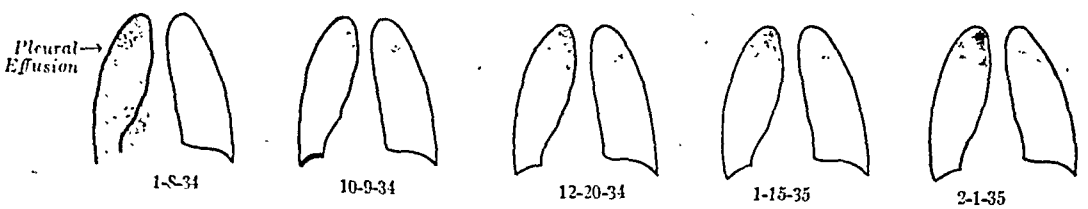
Symptoms: Well, until sudden onset of cough, backache, chest pain and temperature 103° F. Pleurisy with effusion developed for which patient was confined to University infirmary for 6 weeks. Returned home in January, 1934. Continued improvement and patient returned to school in September, 1934.

Physical Examination: October, 1934: Well-developed and nourished girl, aged 19. Chest: left clavicle prominent. Decreased excursion both anteriorly and posteriorly. Impaired resonance left base. No râles.

Temperature: Normal, week of December 22, 1934, and week of January 24, 1935.

Laboratory: Blood sedimentation index: 12 mm., October 13, 1934; 7 mm., December 21, 1934; 25 mm., January 3, 1935; 21 mm., January 11, 1935. Blood count: average count during hospitalization with pleural effusion, 7600 W.B.C., with 70% polys., 25% lymphocytes, 1 to 4% monocytes, 1 to 2% cosinophils. Pleural effusion: 200 cells per c.mm., 97% lymph. and 3% polys. October 8, 1934: 85% Hgb., 5,410,000 R.B.C., 8250 W.B.C., 67% polys., 30% lymph. January 13, 1935: 75% Hgb., 4,700,000 R.B.C., 7400 W.B.C., 75% polys., 24% lymph. Sputum examination: no expectoration. Gastric aspiration not done. Urinalysis negative. Pleural effusion stains. Tuberculosis negative.

Roentgenograms: December 1, 1933: guinea-pig inoculation; pig died, December 22, 1933; no evidence of tuberculosis.



1-8-34 10-9-34 12-20-34 1-15-35 2-1-35

Treatment: Entered sanatorium, February, 1935. Was unhappy. Returned home.

Subsequent course: December 10, 1935. Roentgenograms show marked clearing of infiltrations with bed rest at home.

Case 80551 shows an entirely negative study, and a weight gain of 13 pounds, with a progressive infiltration discovered by fluoroscopic examination.

Case 79831 shows a progressive lesion following pleurisy with effusion. At no time after the original episode of pleurisy with effusion were clinical symptoms present.

Fluoroscopic Examinations. Examination of the lungs by the fluoroscope is economically more practical than the roentgenogram. Where an infiltration or a suspicion of an infiltration is found on the fluoroscopic examination, a film is requested. In individuals of moderate build there is little difficulty in visualizing lesions. Cases 73344 and 69634 show two small infiltrations discovered by this method. Fluoroscopic examination of individuals of moderate or light build has certain advantages over the film. A small lesion on the film is occasionally obscured by the clavicle, which on fluoroscopic examination, because the individual's position is frequently changed, is easily brought into view. The infiltration of Case 69634 was found by fluoroscopic examination, and was thus more easily discerned than on the first roentgenogram taken. The second film was taken during expiration to lower the clavicle and bring the lesion into better view. Study of the excursion of the ribs and diaphragm is not possible with the film. Routine study of the mediastinum in the transverse and oblique views is not economically justified with films. Differentiation between calcified deposits and blood vessels is readily possible on fluoroscopic examination by changing the patient's position.

This work is being done with the regular vertical fluoroscope equipped with the latest type fluoroscopic screen and an exceptionally fine-focus Coolidge tube to give the contrast and detail necessary. The new type "B" Patterson fluoroscopic screen and the XP–3 water-cooled Coolidge tube are used. Five milliamperes are usually required with a kilivoltage ranging from 76 to 85 K.V.P., depending on the size of the patient and the pathologic process present.

TABLE 3.—ROENTGENOLOGIC EXAMINATIONS. CLASSES OF 1937 AND 1938.

Total number positive Mantoux tests using old tuberculin and purified protein derivative, 1440			
Number given roentgenologic examination, 1335. Percentage of positive reactors receiving roentgenograms, 92.7%		Percentage of those receiving roentgenograms.	Percentage of the 5123* students who received the tuberculin test.
Number with no evidence of pulmonary tuberculosis	926	69.4	90.0 (4609)†
Number with first infection type of tuberculosis	333	25.0	6.5
Number with reinfection or adult type of tuberculosis	76	5.6	1.5
Number of positives not receiving roentgenogram, 105	...	...	2.0
	1,335	100.0	100.0
Number with lesions advised to withdrawn from school	21	1.6	0.4

* These figures are arrived at by assuming that all negative reactors would show no tuberculous lesion on Roentgen ray.

† This figure is arrived at by subtracting total number of positives from total tested and adding the number with no Roentgen ray evidence of tuberculosis.

Incidence of Tuberculosis Among Students. Table 3 gives the roentgenogram interpretation of those infected as shown by the positive Mantoux test. Comparing the interpretation of 529 films in September of 1933 with 724 films taken in September of 1934, it is interesting to note the consistency of negative films and the type of lesions found.

	1933, %	1934, %
No evidence of pulmonary tuberculosis	70.7	69.2
First infection tuberculosis	24.2	24.9
Adult tuberculosis	4.9	5.9

Of the 21 withdrawing from school, 15 were advised to leave soon after admission following a short period of observation at the Student Infirmary. Six withdrew the following year because of development or progression of small lesions.

Summary. 1. Pulmonary tuberculosis is seldom discovered in its minimal stage.

2. The pathologic process of minimal pulmonary tuberculosis seldom causes symptoms or physical signs.

3. The diagnosis of minimal tuberculosis is dependent upon periodic Roentgen ray or fluoroscopic examination of the infected as indicated by the Mantoux test.

4. Fluoroscopic examination of the lungs makes possible at a low cost the discovery of significant minimal infiltrations.

5. The methods employed have been efficient in finding pulmonary tuberculosis in its early stages. In no instance of over 4000 individuals being periodically examined has one presented himself because of symptoms of tuberculosis, yet in this group asymptomatic pathologically progressive cases of tuberculosis were discovered.

Conclusions. 1. The eventual institution throughout the country of a program of periodic Roentgen ray or fluoroscopic examinations of all the infected is logical. Consideration of the cost of treatment of tuberculosis, makes a program for early discovery economically justifiable.

2. Would it not appear even more logical to advocate and apply such a case finding program as a public health measure for the general population, rather than limiting it to small groups, and in the end pay the penalty of high morbidity and mortality of late diagnoses? Costs count, and money could more profitably be spent in prevention of symptomatic tuberculosis with its hardships and suffering, than in waiting for patients who are the end-products of the disease and attempting to reclaim them.

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BOOK REVIEWS AND NOTICES

THE AUTONOMIC NERVOUS SYSTEM. Anatomy, Physiology, and Surgical Treatment. By JAMES C. WHITE, M.D., Assistant Professor and Tutor in Surgery, Harvard Medical School; Assistant Visiting Surgeon, Massachusetts General Hospital. Pp. 386; 96 illustrations. New York: The Macmillan Company, 1935. Price, $7.00.

IN the past decade surgery of the autonomic nervous system has found increasingly fruitful application. This monograph is an excellent summary of its results in various diseases, based on Dr. White's personal experience and on a critical evaluation of the work of others. In a field so rapidly growing it becomes necessary to point out not only "those conditions which are suitable for sympathectomy but equally those which are not." This Dr. White does with admirable candor.

In general the objective of sympathetic surgery has been the interruption of either the motor supply of a viscus or the afferent fibers which course in the peripheral sympathetic nerves. An example of the first approach is sympathectomy for spastic peripheral vascular disease, of the second, section of the cardiac sensory pathways in angina pectoris. The utility of preliminary novocaine block as a test of results obtainable by permanent nerve section is stressed.

In addition to practical therapeutic results obtainable, knowledge of underlying pathologic physiology of various diseases which sympathetic surgery has revealed should be of the widest medical interest.

The book is divided into sections on anatomy, physiology and experimental technique, clinical results and surgical technique. There is an adequate bibliography and a good index. G. G.

RADIUM TREATMENT OF SKIN DISEASES, NEW GROWTHS, DISEASES OF THE EYES AND TONSILS. By FRANCIS H. WILLIAMS, M.D. (HARV.), S. B., Massachusetts Institute of Technology; Senior Physician, Boston City Hospital; Fellow American Academy of Arts and Sciences, etc. Pp. 118; 12 illustrations. Boston: The Stratford Company, 1935. Price, $2.00.

THIS small volume on radium therapy is written by one of the pioneers in Roentgenology and Radium Therapy in this country and represents the result of 30 years' experience in the use of radium. It is divided into four parts: Part I deals with the nature and properties of radium, methods of measurement and methods of administration, together with a short account of its use in diseases of the skin and superficial new growths. Part II deals with its use in diseases of the eyes and eyelids and Part III with its use in diseases of the tonsils and other lymphoid tissues in the throat.

Dr. Williams states in his preface that his method is based upon the measurements of the absorption of radiation by different substances used as filters, and by different thicknesses of water used as a standard for the absorption by the soft tissues of the body, thus making possible the selection of the amount and quality of the radiations best suited to a given condition. He describes his early experiments with beta and gamma rays, with tests of their therapeutic value. In the section dealing with the diseases of the eyes and eyelids and the tonsils he describes the instruments used and his

technique in the application of radium. He emphasizes the greater comparative value of irradiation of the tonsils with radium as compared with tonsillectomy.

The book is well printed, is well written and holds the interest of the reader. It contains 12 illustrations of instruments, methods of treatment, and graphs of curves showing absorption of the electrons, etc. Such a concise summary, coming from the pen of a pioneer of such experience with the use of radium and who has had ample opportunity to study his results, should be of invaluable aid to every radiologist. R. B.

THE PARATHYROIDS IN HEALTH AND IN DISEASE. By DAVID H. SHELLING, B.Sc., M.D., The Johns Hopkins University and Hospital, Baltimore. Pp. 335; 26 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, $5.00.

THIS is an unusually good treatise on the parathyroids, dealing in a thoroughly scientific, critical manner with all phases of the parathyroids, anatomical, physiological, chemical, pathological and clinical. The illustrations are effective, the bibliography satisfactory, and the manner of presentation very pleasing. At a time when so many recent writings on the endocrines are appalingly unsound, it is a great pleasure to find a book such as this that can be whole-heartedly recommended. Particularly practical in his discussion of the differentiation between primary and secondary parathyroid hyperplasia with hyperfunction, which should be very useful to internists and to surgeons in determining rational treatment.

I. Z.

THE CAROTID SINUS AND THE CEREBRAL CIRCULATION. An Anatomical, Experimental, and Clinical Investigation. By ERIK LUND ASK-UPMARK, SWEDEN. From the Departments of Neuropathology, Neurosurgery and Anatomy, Harvard Medical School, Boston. Acta Psychiatrica et Neurologica. Supp. VI. Pp. 374; 74 illustrations and 22 tables. Copenhagen: Levin & Munksgaard, 1935. (Price not given).

ONE section of this monograph (pp. 46–181 contains a detailed description of the author's studies of the anatomy of the cerebral circulation and carotid sinus in 61 animals, representing 27 species of mammals, birds, amphibia, and reptiles; it is illustrated with drawing and includes a consideration of communications between external and internal carotid systems. This careful morphologic study furnishes the basis for selecting the animal or animals suitable for certain experiments and discloses fallacies inherent in many experiments that have been made in the past. The remainder of the book comprises a lengthy presentation of some inconclusive experiments dealing with the influence of carotid sinus reflexes upon cerebral blood-vessels; of case records of patients with brain injuries, tumors, or cranial neuralgias; and of some of the voluminous literature dealing with the anatomy and physiology of the cerebral circulation and the carotid sinus, the mode of regulation of the activity of vegetative centers, and the physiologic disturbances associated with lesions involving various parts of the central nervous system and various cranial nerves. These are some of the most vexing problems in physiology and neurosurgery; a monograph on any of them would be most welcome if written by a person of mature experience and judgment, but a monograph dealing with all of them, written by a young clinician as a result of 2 years' incumbency of a Rockefeller Fellowship, seems to the Reviewer to be a monument to the industry of the author rather than a contribution to scientific literature. C. S.

NEW PATHWAYS FOR CHILDREN WITH CEREBRAL PALSY. By GLADYS GAGE ROGERS, Director of Robin Hood's Barn, A Camp School for Children with Cerebral Palsy, and LEAH C. THOMAS, Director of Therapeutics at Robin Hood's Barn. With photographs by NEWELL GREEN. Pp. 167; 12 illustrations. New York: The Macmillan Company, 1935. Price, $2.50.

BASED upon 17 years experience in working with cerebral palsy cases, in the home, hospital and school, the authors of this useful little volume have evolved a hopeful system of treatment in a group of mentally normal but physically crippled children, a group that in point of numbers is second only to that of infantile paralysis. Throughout the book emphasis is placed upon instilling into these children self confidence in order to banish muscular tension. The parent of a spastic child will gain from this book a clearer insight into the child's emotional life, the physical therapist and the teacher will obtain many valuable leads in regard to methods of treatment and educational materials available and the physician will learn the many minute details ordinarily passed over as trivial. In the story so imaginatively unfolded all will observe the happy rewards of infinite patience. As Dr. Robert B. Osgood, in his introduction, so aptly says: "The book is packed with practicality. Through its pages flows an optimism justified by accomplishment." S. R.

COLD SPRING HARBOR SYMPOSIA ON QUANTITATIVE BIOLOGY, VOLUME III. Pp. 359; illustrated. Cold Spring Harbor, L. I., N. Y.: Long Island Biological Association as a part of the work of The Biological Laboratory, 1935. Price, $3.75.

THIS third volume of The Cold Spring Harbor Symposia is concerned with "the interaction of ourselves and things around us with light." It will be recalled that the two previous symposia dealt largely with surface phenomena and some aspects of growth (see Reviews in this journal, 187, 851, 1934 and 189, 577, 1935). The 36 communications deal with photochemistry, chlorophyll, photosyntheses, photosyntropism, bioluminescence, radiation, vision, photosensitization and so on in a highly technical and quantitative manner that would make an adequate review difficult even for the superscientist who possessed adequate knowledge. As a storehouse of the most recent information and a statement of modern theory by competent authorities the book is valuable and has its interest for many.

E. K.

A TEXTBOOK OF BACTERIOLOGY. By THURMAN B. RICE, A.M., M.D., Professor of Bacteriology and Public Health at the Indiana University School of Medicine. Pp. 551; 121 illustrations. Philadelphia: W. B. Saunders Company, 1935. Price, $5.00.

DESIGNED both for the practising physician and the medical student, this text contains excellent and ingenious advice concerning many technical procedures adapted to limited time, material, and equipment. A shortened textbook, emphasizing the salient points of diagnosis, prognosis, etiology, specimen collection, interpretation of laboratory findings, specific therapy prophylaxis, etc., this simplified account serves only as a bare introduction to the science of bacteriology. Certain biochemical and physical phenomena are explained too diagrammatically. The importance of the changing equilibrium between host and parasite is not stressed. There are no specific references to the source material. A compact table presents the choice of culture media for simple diagnostic bacteriologic work for eleven classes of

pathogenic organisms (including fungi). There is also a compendium of the various routes of inoculation and the customary uses of each. Five appendices contribute to the value of the book. One deal with special bacteriology which includes the urine, the gross appearance of infected wounds, decubitus ulcers, chronic focal infections and pyrogenic substances in distilled water. Common errors in the technique of collecting samples are pointed to, as the author describes exactly what should be done in each case. There are sections on federal and postal regulations for the sale and transportation of viruses, serums, toxins, etc., and on the technique of practical disinfection. E. B.

BODY WATER. The Exchange of Fluids in Man. By JOHN P. PETERS, M.D., Professor of Internal Medicine, Yale University School of Medicine. Pp. 405; 5 illustrations and 15 tables. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

THIS scholarly book discusses a subject of great importance to an understanding of many physiological and pathological processes. Water is the most abundant constituent of living things; it has unique and remarkable properties of which not the least is its capacity to dissolve so many different chemicals. Life depends upon constant interchange between the cells of the body and its fluids, the blood, lymph and interstitial fluid. It is this exchange as it occurs particularly in man with which the book deals. There are chapters on the chemical forces that control the exchange of water and of solutes; on the nature and movements of interstitial fluid and of lymph; on the exchanges between blood and interstitial fluid, and between various cells and fluids; on transudates; on the water produced through the oxidation of foodstuffs; on the losses of water through the skin and the respiratory passages; and on the exchanges in the alimentary tract.

These chapters constitute a background for the discussion of the functional pathology of renal disease to which is devoted over one-third of the monograph. In the chapter on the general nature of renal activity the author emphasizes a rôle of the kidney not always properly appreciated in clinical medicine; namely that the kidneys serve not only as excretory organs but that they also conserve selectively, for the further use of the organism, a considerable variety of substances, of which glucose is probably the most familiar example. In states of renal insufficiency the disturbances are due not solely to retention of substances that are normally eliminated, but also to elimination of substances that are normally conserved. In further chapters is discussed the excretion of water, of salts, and of other solutes; and the nervous and hormone control of urine excretion.

For the reader who would pursue in more detail any of the topics there is appended a bibliography of nearly 900 titles. B. L.

DISEASES OF WOMEN. By HARRY STURGEON CROSSEN, M.D., F.A.C.S., Gynecologist to the Barnes Hospital, St. Louis Maternity Hospital, and St. Luke's Hospital, etc., and ROBERT JAMES CROSSEN, M.D., Instructor in Clinical Gynecology and Obstetrics, Washington School of Medicine, etc. Pp. 999, 1058 illustrations including one color plate. Eighth Edition, entirely revised and reset. St. Louis: The C. V. Mosby Company, 1935. Price, $10.00.

THIS edition appears in a new and attractive style of paging and binding. The revision shows a thorough evaluation of the contributions to gynecologic literature of recent years with the inclusion of much new material. The second chapter, which discusses gynecologic pathology, is developed to an

unusual degree. A very logical arrangement of the subject matter brings out in an orderly sequence all morbid conditions of the pelvic structures. Meyer's views on the etiology of certain ovarian tumors are freely quoted. This section is profusely illustrated with photomicrographs of unusual merit. The present edition should sustain the popularity of this standard work. P. W.

THE TREATMENT OF ACUTE POISONING. By H. L. MARRIOTT, M.D., M.R.C.P. (LONDON), Resident Medical Officer, The Middlesex Hospital, London; Assistant Physician, The Miller General Hospital, Greenwich. Pp. 45; 15 illustrations. London: John Murray, for the Middlesex Hospital Press, 1935. Price 5s.

IN a brief and easily readable monograph, the author discusses the treatment of acute poisoning and the therapeutic measures which he has found most satisfactory. He believes that in emergency cases, much valuable time is lost in attempting to recall and administer a specific antidote. It is pointed out that this is seldom necessary since the treatment of all types of poisoning is fundamentally similar and consists of (1) removal or neutralization of the poison and (2) counteraction of its effects. This idea of simplicity is one to be highly recommended, although the book contains little else which is not already familiar to the average physician. L. B.

DER GEBURTSTOD (MUTTER UND KIND). By DR. SIGISMUND PELLER, Pp. 110; 56 tables. Wien: Franz Deuticke, 1936. Price, M. 5.

THE various factors causing Infant and Maternal Mortality are here ably discussed. Not only has the subject been handled by analysis of published statistics but a review of the causes of death is presented from the standpoint of preventive medicine in its broadest sense. Peller feels that the problem of natal mortality is primarily one of physiology and social hygiene, and regards the possibility of reducing the natal mortality of infants to 1% and first week mortality to 0.5% as an attainable end.

Regarding maternal mortality he feels that the specific and non-specific causes of death have not been sufficiently differentiated in various countries to make comparisons equable. The abortion problem, as he points out, further clouds the true picture of obstetrical death rates. Abortion as a single cause of maternal death holds the center of the stage in the world over. P. W.

AUTOBIOGRAPHY, SIGMUND FREUD. Translated by JAMES STRACHEY. Pp. 153; 1 illustration. New York: W. W. Norton & Co., Inc., 1935. Price, $2.00.

THIS monograph is an enlarged and revised edition of the essay published in 1925 in Die Medizin der Gegenwart in Selbatdarstellungen. It is not so much an autobiography as an account of the historical development of Freud's ideas, all of which are presented very sketchily because of lack of space. To those who will be led to read this book in order to obtain a true autobiography of Freud, the work will be a real disappointment. There is no attempt at self-analysis, and no real autobiographical material, except insofar as it affects the development of the theory of psychoanalysis.

One feature of the book is extremely interesting, viz.: Freud's early interest in organic neurology. He was well-trained in physiology, wrote an excellent monograph on cerebral diplegia, one of the first to advocate the use of cocaine as a local anesthetic, and made on of the first diagnoses of

acute polyneuritis. Organic neurologists will probably point to these facts to prove that organic neurology is the backbone of all neuropsychiatry, when in truth it only demonstrates that Freud's was a very keen and alert mind which was capable of superior work in whatever field it was interested.

The account of the birth of analysis, its development from hypnosis, and the schism between Breuer and Freud is told frankly. Freud does not hesitate to discuss freely his quarrels with his other dissenting disciples such as Jung and Adler, but none of his accounts become polemic. Some account is given of the struggle for recognition of psychoanalysis, but none of it bitter.

The book is very readable. The translator has done such an excellent job that one is rarely aware of reading a translation. The book may be recommended for a sketchy account of Freud's theories, and for a few fragments of Freud's intimate life. B. A.

NEW BOOKS.

The Microscopic Anatomy of Vertebrates. By GEORGE G. SCOTT, PH.D., Professor of Biology in the City College, New York City, and JAMES I. KENDALL, PH.D., Instructor in Biology in the City College, New York City. Pp. 306; 167 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $3.75.

Medical Mycology. Fungous Diseases of Men and Other Mammals. By CARROLL WILLIAM DODGE, PH.D., Mycologist, Missouri Botanical Garden; Professor, Henry Shaw School of Botany, Washington University, St. Louis. Pp. 900; 142 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, $10.00.

Clinical Miscellany, Volume II, 1935. The Mary Imogene Bassett Hospital, Cooperstown, N. Y. By NINE CONTRIBUTORS. Pp. 218; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $3.00.

Bibliography on Blood Transfusion, Vol. I. (International Bibliography on the Problems of Blood Transfusion and the Theory of Blood Groups, 1900–1933.) By DR. E. KOENIG. Pp. 226. Leningrad: Professor E. Hesse, 1935. Price, 12 p., 50 k.

Folk-lore from Adams County, Illinois. By HARRY MIDDLETON HYATT, M.A. (OXON.), D.D., Director of the Alma Egan Hyatt Foundation; Officier d'Académie Française; Officier de l'Ordre de la Couronne, Royale de Belgique. Pp. 723. New York: Alma Egan Hyatt Foundation, 1935. Price, $6.00.

Das Hämorrhoidalleiden. Seine Komplikationen und Deren Behandlung. By DR. KASPER BLOND and DR. HERBERT HOFF. Pp. 121; 50 illustrations, many in colors. Wien: Franz Deuticke, 1936. Price, Paper, M. 12; Bound, M. 14.40.

Differentialdiagnose in der Inneren Medizin, Part I. By PROFESSOR DR. MED. O. NAEGELI, Direktor der Medizinischen Universitatsklinik, Zürich. Pp. 216; 55 illustrations, some in colors. Leipzig: Georg Thieme, 1936. Price, M. 9.60.

The Diagnosis and Treatment of Diseases of the Peripheral Arteries. By SAUL S. SAMUELS, A.M., M.D., Chief of the Clinic for Peripheral Arterial Diseases, Fourth Division, Bellevue Hospital, New York; Chief of the Department of Arterial Diseases, Stuyvesant Polyclinic Hospital, New York, etc. Pp. 260; 51 illustrations. New York: Oxford University Press, 1936. Price, $3.50.

Lobar Pneumonia and Serum Therapy. With Special Reference to the Massachusetts Pneumonia Study. By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc., and RODERICK HEFFRON, M.D., Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 91; 10 figures, 1 plate. New York: The Commonwealth Fund, 1936. Price, $1.00.

You Must Eat Meat. Fancies, Foibles and Facts about Meat. By MAX ERNEST JUTTE, M.D., Formerly Lecturer on Stomach and Intestinal Diseases, New York Polyclinic Medical School, etc. Pp. 164; illustrated. New York: G. P. Putnam's Sons, 1936. Price, $2.00.

Le Sang des Hypertendus. By GEORGES CARRIÈRE, Professor de Clinique Médicale, and CLAUDE HURIEZ, Chef de Clinique Médicale, a la Faculté de Médeciné de l'Université de Lille. Pp. 386; many tables. Paris: G. Doin et Cie, 1936. (No price given.)

Glandular Physiology and Therapy. A Symposium Prepared Under the Auspices of the Council on Pharmacy and Chemistry of the American Medical Association. Pp. 528; illustrated. Chicago: American Medical Association, 1935. Price, $2.50.

American Chamber of Horrors. The Truth about Food and Drugs. By RUTH DE FOREST LAMB. Pp. 418; illustrated. New York: Farrar & Rinehart, 1936. Price, $2.50.

A History of Science, Technology, and Philosophy in the 16th and 17th Centuries. By A. WOLF, Professor and Senator, University of London; Head of the Department of History and Methods of Science, etc. With the Coöperation of DR. F. DANNEMANN, Professor in the University of Bonn, and MR. A. ARMITAGE, of University College, London. Pp. 692; 316 illustrations. New York: The Macmillan Company, 1935. Price, $7.00.

For and Against Doctors. An Anthology compiled by ROBERT HUTCHINSON and G. M. WAUCHOPE. Pp. 168; illustrated. Baltimore: William Wood & Co., 1935. Price, $2.00.

The Hair and Scalp. A Clinical Study (With a Chapter on Hirsuties). By AGNES SAVILL, M.A., M.D. (GLASG.), M.R.C.P.I., Consulting Physician to Fitzroy Square Skin Hospital, etc. Pp. 288; 54 illustrations. Baltimore: William Wood & Co., 1935. Price, $5.00.

The Foot. By NORMAN C. LAKE, M.D., M.S., D.Sc. (LOND.), F.R.C.S. (ENG.), Senior Surgeon and Lecturer on Surgery, Charing Cross Hospital; Surgeon, Bolingbroke Hospital, etc. Pp. 330; 95 illustrations. Baltimore: William Wood & Co., 1935. Price, $4.50.

NEW EDITIONS.

A Manual of the Common Contagious Diseases. By PHILIP MOEN STIMSON, A.B., M.D., Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Visiting Physician, Willard Parker Hospital, etc. Pp. 437; 53 illustrations and 3 plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $4.00.

Delafield and Prudden's Text-book of Pathology. Revised by FRANCIS CARTER WOOD, M.D., Director of the Pathological Department, St. Luke's Hospital, New York; Director of the Institute of Cancer Research, Columbia University, New York. Pp. 1406; 839 illustrations and 22 full-page plates, many in color. Sixteenth edition. Baltimore: William Wood & Co., 1936. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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DISORDERS OF MENSTRUATION.

BEFORE discussing a few of the deviations from normal in the process of menstruation it might be pertinent to state that in spite of the tremendous advances which have been made in the study of this phenomenon, the actual mechanism has not been definitely determined in all its details. After discussing the various theories of menstruation that have been elaborated during the past century, Fluhmann[1] presents what he believes is the accepted theory at the present time. The sex hormone (prolan) of the anterior hypophysis stimulates the development of an ovarian follicle. As this matures it produces estrin which in turn causes the endometrium to grow. After full development of the Graafian follicle, ovulation takes place and a corpus luteum is formed in the remains of the follicle. The corpus luteum produces a secretion called "progestin" which controls the development of the characteristic premenstrual changes in the endometrium, and in addition estrin is formed in greater amounts than before. This estrin production causes a progressive inhibition of the anterior lobe of the pituitary gland so that the amount of prolan available gradually diminishes. Finally estrin reaches its peak and correspondingly the amount of prolan has diminished to the point that it is insufficient to maintain the corpus luteum. This structure undergoes degeneration which results in the cessation of estrin production and thus a breakdown of the endometrium occurs which is known as menstruation. The absence of estrin now releases the inhibition of the anterior lobe of the pituitary which again secretes its sex hormone to stimulate the development of a follicle in the ovary for the next menstrual cycle.

Shaw[2] has studied the material removed at operation in 36 cases in which the cyclical changes in the ovaries could be examined and in 70 cases in which the cyclical changes in the endometrium could be

observed in order to determine the relation between ovulation and menstruation in women who menstruate regularly with a normal rhythm. He had previously shown that irregular bleeding is characterized by departures from the normal relationship of these two processes. In the present study the time relations of ovulation and menstruation have been investigated with the use of the method of identifying recently ruptured follicles in the ovaries in women who give reliable histories. It has been shown that ovulation is restricted to about the 14th day of the cycle. There is some variation in the time of ovulation but the variation is probably not more than 2 days. A study of the condition of the corpora lutea at other stages of the cycle confirms this view. Indirect proof as to the time of ovulation can also be obtained by examinations of specimens of the endometrium. It has been shown that the secretory phase of the endometrium develops after the 14th day of the cycle. The specific features of the secretory phase are never seen before this time.

For many years, particularly before the present theories of menstruation were offered, it was thought by many gynecologists that frequently irregular and profuse menstruation was due to some pathologic change in the muscular wall of the uterus, hence the terms "chronic metritis," "myopathic bleeding" and "fibrosis uteri" were convenient labels for a condition which was not well understood. Refuting such concepts is the work of Baker,[3] who studied the collagenous tissue of the myometrium of 40 uteri obtained at necropsy and 19 removed at operation. The material consisted of 13 uteri from nulliparas dead from accidental causes, 7 from nulliparas dead from acute infectious causes, 14 from cases in which death was caused by a chronic disease, 10 from cases of acute pelvic inflammation and 15 from cases in which there was a history of abnormal bleeding. Blocks were taken from various parts of the uterine wall and he observed that with the advance in the age of the patient there occurs within the uterine wall a gradual increase of collagenous fibers which ultimately replace the greater part of the muscle. Neither localized nor systemic acute processes have any marked effect on the uterine wall. Chronic diseases have no effect on the uterine wall of young nulliparas but hasten the age of fibrosis in older nulliparas. The uterine arteries show less pronounced age changes than does the musculature. A study of the uteri from cases of idiopathic bleeding in young women showed no increase of fibrous tissue or abnormal arterial changes that would distinguish them from the normal controls. In the elderly women there was often moderate to extreme fibrosis and a varying degree of arterial change, but these alterations were not more prominent than in the non-bleeders of corresponding age. In brief, therefore, he found no satisfactory evidence that fibrosis of the uterine wall is responsible for uterine hemorrhage.

Irregular Shedding and Ripening of the Endometrium. For a number of years Traut and Kuder[4] have found it increasingly difficult to account for the clinical history, as well as the histologic findings of some cases of functional uterine bleeding on the basis of the usual endometrial hyperplasia syndrome. They have come to the conclusion that there are other clinical entities which cause or are associated with metrorrhagia and although they may be hormonal in origin, they are quite

distinct from hyperplasia. They present two entities, one of which has not hitherto been described while the other has been recognized only in the German literature. The usual type of functional bleeding is regarded as being due to endometrial hyperplasia which results from a hypersecretion of estrin or lack of its neutralization by a decrease or absence of luteal hormone. In the condition which they describe as irregular shedding of the endometrium there is an aberration of the secretory or corpus luteum phase of menstruation. In 1 year they found that about 10% of their patients who had functional bleeding belonged in this group. These patients ranged in age from 23 to 50 years and all gave a history of normal periods until they came under observation because of a prolonged and profuse period or of recurrent bleeding immediately following what was supposed to have been a normal menstrual period. Estrin determinations of the blood showed almost complete lack of this hormone. The genital organs were normal and no constitutional disease was noted in any case. Curettage shows a definite and characteristic histologic picture. The stroma is shrunken and composed of many deeply basophilic spindle-shaped nuclei. The spiral arterioles are usually dilated and engorged and occasionally thrombosed. The epithelium is obviously in the corpus luteum or secretory phase which distinguishes the specimen from hyperplasia, which is just as markedly non-secretory in type. In normal menstruation the shedding of the spongiosa is a progressive phenomenon in the sense that there is focal shedding at a given time and that subsequently other foci bleed and shed in succession, so that the duration of the menstrual period is dependent upon the rapidity with which the various local processes succeed one another. It would seem probable that in this type of menorrhagia we have a very much prolonged menstrual period. As the corpus luteum is in the ascendancy during this phase of the cycle, it would seem that it had some causative effect on such a disturbance of function, although the explanation must remain theoretical for the time being. The treatment consists merely in the usual curettage, after which bleeding ceases.

The second entity which they describe differs from both the hyperplasia and the irregular shedding groups, for these represent two different phases of ovarian activity: the first, the Graafian follicle phase, and the latter, that of the corpus luteum, whereas the one now to be considered (irregular ripening of the endometrium) represents both a mixture of both proliferative and secretory phases. In their study of 100 patients with functional uterine bleeding, they found this mixed picture in 21, hyperplasia in 68 and irregular shedding in 11. Histologic examination in these 21 cases showed an endometrium which in the peripheral zone showed areas which were non-secretory and others which were just as definitely secretory. The impression which they gained from a study of the sections was that of a patchy or irregular corpus luteum effect in an endometrium otherwise in the proliferative phase, hence they call this condition "irregular ripening." These patients, like those which have irregular shedding of the endometrium, have responded promptly to curettage and have not had a recurrence of the disease. They are at a loss to explain the non-recurrence, because they feel that the disease has its origin in a quantitative imbalance of

the ovarian hormones which should not be remedied in all cases by simple curettage. The above study is of interest to both the gynecologic pathologist and the endocrinologist; but to the practical operating gynecologists the important point is that all three conditions mentioned respond to curettage, although endometrial hyperplasia may occasionally require some irradiation as well.

Menstrual Disturbances Associated With Low Metabolic Rates. A group of patients who had amenorrhea, oligomenorrhea or menorrhagia and low basal metabolic rates were treated by Haines and Mussey[5] at The Mayo Clinic with carefully regulated oral doses of desiccated thyroid glands. To determine the effectiveness of desiccated thyroid alone in the treatment of these conditions, no patients who received any other form of treatment were included in the study. Definite improvement in the menstrual flow was obtained in 72% of the cases in which there was amenorrhea; in 55% in which there was oligomenorrhea, and in 73% in which there was menorrhagia. Aside from whether or not there was an improvement in the menstrual disturbances, about 75% of the entire group of patients reported improvement in their general health after elevation of the basal metabolism to within the average normal limits. There is sufficient individual variation in the daily dose of desiccated thyroid to make it necessary to hold the basal metabolic rate at the optimal level for the individual patient. Therefore patients were not treated unless they could be kept under observation long enough to work out the necessary dosage. In this group the dosage varied from ½ to 3 grains daily. Because most patients feel best if the basal metabolic rate is held at about −3 to −8%, this level was aimed at in the treatment. It seemed as effective as higher levels in the treatment of menstrual disturbances and was much less likely to result in uncomfortable symptoms, such as palpitation, diminished heat tolerance and weakness. As a rule, thyroid treatment has to be continued for an indefinite period. They have noted that when patients improve on thyroid medication, the discontinuance of the treatment is commonly followed by lowering of the metabolic rate and a relapse to their former condition.

Treatment of Menstrual Irregularities. It is often of great importance to obtain a specimen of endometrium before instituting treatment of functional uterine bleeding in order to differentiate the physiologic responses of the mucosa to one or another type of hormone stimulation. Novak[6] states that the endometrium is the registering board of ovarian endocrine activity and its microscopic study often yields much more useful information than blood or urine hormone studies. For this purpose he has devised a suction curette apparatus which can be used without anesthesia and without discomfort to the patient. The instrument is about the size of the cannula which is used in the Rubin test and is connected with a power suction machine. The test can be done as an office procedure, but strict asepsis should be maintained.

Antuitrin S, an extract of the urine of pregnant women, was administered by Smith and Rock[7] to 56 patients with dysfunctional uterine bleeding. Of these, 28 were cured, 22 benefited and 6 were unrelieved. The cessation of bleeding accompanied treatment so often and in many cases so rapidly as to leave little doubt as to the specificity of the

hormone. These cases usually show ovaries which fail to contain a corpus luteum which secretes the hormone which is supposed to prevent uterine bleeding. The logical treatment, therefore, would be the administration of corpus luteum. Since satisfactory preparations of corpus luteum are not available for clinical use, several investigators have used the extract of urine from pregnant women which contains a luteinizing principle causing the formation of corpora lutea in the ovary. This extract is known by several names, such as antuitrin S, prolan B, follutein, etc. The usual treatment consists of from 2 to 6 intramuscular injections of 5 to 10 cc. over a period of from 4 to 10 days. Each cubic centimeter represents 100 rat units, a rat unit being the smallest amount that will cause luteinization in the ovary of the immature rat. The reactions from the injections are often severe and occur in the form of chills, headache, fainting, nausea, vomiting and fever occurring within 12 hours after injection. They occurred in 21% of the injections in this series. The injections seem to be more effective if given while the patients are bleeding than if given as a prophylactic.

Bakacs[8] has been able to control abnormally profuse menses in 82% of the cases by the injection of parathormone and calcium gluconate, whether the case is simple hypermenorrhea or metropathia hemorrhagica. He uses a preparation called Paracals, which contains 50 units of parathyroid hormone and 100 mg. metallic calcium in the form of calcium gluconate, which is given as an intramuscular injection in the gluteal region. It is of value as a prophylactic treatment in about 70% of cases if injected for 4 to 6 days before the expected period. He believes that the value of the parathyroid extract is not due alone to its action upon the calcium, but that it has some value of its own.

The functional menstrual irregularities in young women have been divided into two groups by Drips,[9] according to the predominant symptom, namely amenorrhea and menorrhagia. In a group of 244 cases of the amenorrheic type treated at The Mayo Clinic which were observed for 1 year, it was found that low voltage irradiation of the ovaries and the hypophysis has proved to be the most valuable therapeutic agent in reëstablishing the menses. It has made pregnancy possible in the more severe cases in which organotherapy failed. In the menorrhagic group, comprising 213 cases, it was found that small doses of radium within the uterus constitute the most effective treatment in the more intractable cases in which organotherapy has failed. It should be emphasized that at this clinic irradiation is not administered until medical measures have been tried without success.

Mazer and Spitz[10] are also enthusiastic about the value of low voltage irradiation of the pituitary gland and the ovaries. They report that 23 of 47 women suffering from severe amenorrhea have been menstruating regularly without the stimulus of incidental pregnancy for periods averaging 2.3 years following such treatment. Eight of 15 women suffering from a milder form of amenorrhea (oligomenorrhea) have likewise been restored to normalcy. In the patient of average size, the technical factors are 127 K.V., 5 M.A., 14 inch distance, 5 mm. aluminum filter for 3 to 5 minutes. This is equivalent to $7\frac{1}{2}$ to $12\frac{1}{2}$ S.E.D. or 50 to 80 R. This dosage is varied according to the size of the abdo-

men and the thickness of the abdominal wall. The central ray (in the pituitary exposure) enters just above and posterior to the midpoint of a line drawn between the outer canthus and the external auditory canal. In nearly half of the patients the pituitary gland and the ovaries were treated simultaneously; in the others the exposures were made alternately at 3- or 4-day intervals. The results were approximately the same in both groups. While roentgenologists do not hesitate to treat the pituitary gland, many of them are reluctant to expose the ovaries even to mild irradiation because of reports that in some cases a temporary amenorrhea has become permanent because of such treatment. It is possible that these amenorrheic women would have developed amenorrhea of a permanent type even without such treatment. In order to determine the effect of their treatment on the ovaries they carefully recorded for a period of nearly 3 years after the treatment, the menstrual cycles of 11 regularly menstruating women, and in none of them was the menstrual rhythm affected by irradiation in doses within the limits indicated above. Nevertheless, they caution that the margin between the safe and the harmful dose is probably a very small one.

Keene and Payne[11] state that in many of the milder forms of functional uterine bleeding, the blood loss is insufficient to require treatment. Change of climate, occupation or mode of living will occasionally be followed by a resumption of normal menstruation, or the menstrual irregularity may cease for no explainable reason. They have found that the use of antuitrin S has been of value in about two-thirds of the patients under 30. Beyond this age the treatment becomes less useful as the age increases, it being almost without value after the age of 40. The present teaching concerning the causes of functional bleeding casts discredit upon curettage as a therapeutic measure and explains its frequent failure, but curettage may be of value in certain cases, particularly in young women, where one might hesitate to use radium. Some of these patients will be temporarily benefited or cured. With temporary relief the curettage may be repeated with the hope that sooner or later normal menstruation will become established. After 40 and in younger women, when other methods have proven unsuccessful, radium or Roentgen therapy is indicated. They prefer radium because its dosage can be more accurately regulated and the beneficial effects are in part due to its local action upon the uterine bloodvessels. It should be remembered that profoundly anemic patients react poorly to both radium and the Roentgen ray, and either form of irradiation should be withheld until the blood has been improved by transfusion and other appropriate treatment. Radium may be dangerous in patients who have had a previous pelvic operation, since an intestinal loop adherent to the uterus may be seriously damaged by the rays. The absence of intermenstrual pelvic pain and severe dysmenorrhea is characteristic of functional bleeding. Their experience stresses the point that when pain is an associated symptom, some organic lesion is usually present, even though examination fails to reveal it, and operation is preferable to radium therapy. With surprising frequency the wisdom of this decision will be proven when the abdomen is opened. The highly nervous woman is a poor subject for irradiation because

of the distressing sequelæ which frequently attend the induced menopause. In this type of woman hysterectomy with ovarian conservation yields better results. Radium is rarely indicated in the treatment of patients under 20. When it is found necessary, the initial dose should not exceed 200 mg. hours. Between 20 and 30, their results show that a dosage of 400 mg. hours can be administered safely. This dosage will be more than 80% efficient in the control of bleeding, but a few patients will develop a temporary amenorrhea of a few months' duration. Should the bleeding persist, the dosage can be increased by 100 mg. hours. Their analysis of the group between 30 and 40 brings out the important fact that with increased dosage there is a rapidly increasing incidence of menopausal manifestations. With a dosage of between 800 and 1200 mg. hours, permanent amenorrhea occurred in 56% and severe menopausal symptoms in 47% of the patients. An initial dosage of 300 mg. hours will control the bleeding in 80% and without permanent amenorrhea. Should reradiation be necessary, an application of not more than 400 mg. hours should be administered, and if this fails, they favor hysterectomy with conservation of ovarian function rather than increased radiation. Functional bleeding occurs most frequently between 40 and 50, and because these women are approaching the time when, in the normal course of events, functional activity will cease, the administration of a menopausal dose of radium has come into common usage. They believe, however, that this is a mistake because of the high incidence of severe menopausal symptoms. In women near 40 they are using a 400 mg. hour dosage. Should this and a reradiation dosage of 500 mg. hours fail, a hysterectomy is advised. In women near 50, increased radium dosage can be used because the incidence of severe menopausal symptoms attending it will be more nearly like those of the uninduced menopause. Between 50 and 60, the results of radium therapy are almost ideal, and maximum dosage can be given because severe menopausal reactions rarely develop.

Dysmenorrhea. The satisfactory treatment of severe dysmenorrhea has always been a problem and in years gone by numerous anodyne drugs have been recommended, many of which were found to be without value, while others helped but slightly. With the advent of the surgical era various types of minor operations were advised, and while some were satisfactory in certain cases, there remained the stubborn severe type of dysmenorrhea which seemed refractory to all forms of treatment. In recent years, following the successful employment of presacral sympathectomy for the relief of pelvic pain in cases of inoperable cancer of the uterus, the suggestion was made that this same operation might be of value in dysmenorrhea and numerous reports indicate that it is being tried and with encouraging results.

Counseller and Craig[12] believe that the results obtained from resection of the superior hypogastric plexus would indicate that the primary etiologic factor in dysmenorrhea is dysfunction of the pelvic sympathetic nervous system. When this dysfunction is corrected by resection the benefits are permanent, while the functions of normal menstruation and childbirth are not disturbed. If menstruation has been abnormal in amount and duration, there is a marked tendency for menstruation to become normal.

Adson and Masson[13] agree that the presacral fibers undoubtedly carry afferent sensations of pain, but it is their opinion that the relief of pain in functional dysmenorrhea is obtained not only by cutting the pain fibers but from interruption of efferent fibers in the presacral group, which supply the bloodvessels in the genitalia and the musculature of the uterus. In order to relieve all pain arising in the region of the ovaries, they state that it would be necessary to strip the ovarian arteries by periarterial sympathectomy or by dividing the vessels. Thus, by resecting the presacral nerve in conjunction with periarterial sympathectomy of both ovarian arteries, it should be possible to relieve pain both in the uterus and in the ovaries. This combined operation is not done by many operators so far as the literature would indicate. Most of the reports that we have seen are concerned with presacral resection alone. Adson and Masson divide dysmenorrheas into two groups: the true functional type without organic lesions, and those which are complicated by gynecologic lesions. As a rule, therefore, at The Mayo Clinic, these patients are operated upon by both the gynecologic and the neurologic surgeons. Before any type of sympathectomy has been performed the surgeon explores the pelvis and corrects the pathologic condition, and if not sufficient change is found to explain the pain, resection of the presacral nerve is performed as a single operation, or it is combined with resection of the lumbar trunk or with periarterial sympathectomy of the ovarian arteries. They have not done many presacral resections but they are convinced that the operation is quite useful, judging from the results obtained in the cases which they have operated upon.

Based on an experience of 21 cases, De Courcy[14] strongly recommends the procedure for the relief of obstinate cases which have proved quite resistant to ordinary measures. Good judgment in the selection of cases is a prime requisite. He uses the same technique as others have described and has had no case in which pain has been unrelieved. He has found that menstruation regularly takes place within 48 to 72 hours after operation, no matter at what time in the menstrual cycle it has been performed. Most of his patients have had to be catheterized for 2 or 3 days, but none of them has had further bladder trouble. Several of his patients became pregnant subsequent to operation.

Wetherell[15] believes that this operation belongs in the domain of the gynecologist; one who is able to analyze the individual case and to determine whether everything has been done in a medical way for the relief of the dysmenorrhea. Furthermore, it is necessary that he be able to judge the necessity for the removal of gross pathologic conditions if found present. It is not merely a question of whether the surgeon is able to resect the plexus, but whether the individual case has been fairly studied and that nothing remains to afford relief except surgery. In the light of previous radical treatment, such as radiation, hysterectomy, or the use of opiates, he believes this operation to be a conservative one, but the ever present possibility of a mortality must be kept in mind and the operation advised only in those cases in which there is definite evidence that no other treatment will help. The operator's experience should be such, that in cases of secondary dysmenorrhea requiring other surgery, the operation will be performed with such

rapidity as will allow enough time for the added nerve resection without jeopardizing this patient. He has found no deleterious effect on libido or future pregnancy as a result of the operation.

As a result of his small experience with this operation, Keene[16] believes that it has a place in the treatment of properly selected cases of functional dysmenorrhea, but its adoption is warranted only when less radical measures have failed. In organic dysmenorrhea, presacral resection may be used with advantage to supplement operations on the pelvic organs. He has found that the operation is ordinarily not difficult, but conditions may be encountered rendering its performance not only tedious but also hazardous.

Kindel[17] has performed the operation in a series of 39 cases with 2 deaths. There were 4 cases which could not be followed although the immediate results were good. Of the remainder excellent results were obtained in 14, in 4 the results were classified as very good, good in 6, fair in 4 and there was no benefit in 5. He also cautions that this procedure should be employed only in carefully selected cases. It should not be used as an immediate procedure, particularly in adolescent girls whose first few periods may be irregular and painful. One-fourth of the patients in this series had been previously operated upon without relief of their dysmenorrhea. It can be clearly seen from all of the above reports that this operation is not to be lightly recommended to the "run of the mill" patient with dysmenorrhea, but when one of the cases of severe type appears and all other types of treatment have failed, this operation may be recommended with a reasonably good expectation of relief from further pain.

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DERMATOLOGY AND SYPHILOLOGY

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SOME CURRENT CONCEPTIONS OF CUTANEOUS ALLERGIC MANIFESTATIONS.

Theory of Allergic Manifestations. The new-born science of allergy is going through a variety of very interesting changes and one might say experiences in its efforts to apply and accommodate itself to the behavior of the skin. It is proposed in this summary to editorialize to a certain extent on the publications of the past several years rather than to attempt a complete and meticulous review of a literature so enormous that even constant special attention can scarcely keep track of its innumerable ramifications.

One of the best evidences of flux in a field of knowledge is confusion in terminology and controversy over names. The prime example of this with respect to allergic phenomena in the skin is the discussion which has waged about the term eczema. Eczema has always been a subject of controversy among dermatologists, the morphologic school attempting morphologic differentiation, the histopathologic school attempting histopathologic differentiation, and more recently the newer etiologic and functional viewpoint attempting differentiations based on multiple causative factors and on functional changes as distinguished from structural alteration or clinical lesion. With a perspective of 20 years it is particularly interesting to observe how the old arguments over the significance of oozing, crusting, fissuring, thickening or lichenification, and similar signs as differentiating between dermatitis and eczema, have gradually branched out on the European side of the Atlantic into an effort to define eczema as a specific reaction on the part of a specific group of cells, namely, the epidermis. As the more or less opposing side of the argument, emphasis has been laid by another group on the differentiation of eczema from dermatitis on the score of an individual predisposition in the former, a background, a general susceptibility, or the interplay of various elements including infection,

vasomotor and sweat function, neurogenous factors and functional disturbances in various structures of the body as well as focal or localized infections (other than cutaneous). These are regarded by this group as the setting for the stage or the etiologic scene, so to speak, on which the actual dermatosis develops.

In the main we believe it may be said that within the functional group the allergists have tended at first to emphasize the local factors in opposition to or with a reluctant disposition to compromise with those who have continued to insist upon the great importance of the individual makeup and the predisposing background of the patient. In Europe, some of the most striking and particularly satisfying advances have been made by the Jadassohn and Bloch school of dermatology. The demonstration by them of specific cutaneous allergic susceptibility, their emphasis upon the localization of the shock structure in contact dermatitis to the epidermis and the definiteness with which they have been able to define the exciting or "trigger pulling" causes in many previously ill-defined eczematous manifestations has aroused general admiration and has very properly given their pronouncements extraordinary weight. For other than European, or one might almost say German-speaking students of cutaneous disease, however, the appreciation of and general acceptance of these views has been retarded by a difficulty involving terminology. The limitation or appropriation of the term "eczema" traditionally carrying for English-speaking people at least an aura of the indefinable or *ipso facto* constitutional background, has obscured rather than clarified the situation, at least for the time being. It should be clearly understood by all students of cutaneous allergic phenomena that eczema in the mouth of European, and particularly of German or Swiss trained, dermatologists means a dermatitis resulting from the specific irritation of a specific group of epidermal cells and nothing else whatever. Other forms of inflammatory reaction on the part of the skin are not in the estimation of this group of observers to be rated as having title to the name eczema, however much they may seem to conform in clinical appearance to the conventional morphologic and structural appearances of what for English and American dermatologists has been eczema for considerably more than half a century. On the other hand, dermatitis with purely locally acting causes, which disappeared on removal of the irritant, and which for the English and part of the Viennese school has been dermatitis and not eczema, has been included by the new group in "eczema." For English-speaking dermatologists, and some Europeans until very recently, no such specific allergic sensitivity on the part of a particular group of epidermal cells was recognized. Eczema for them meant a morphologic and evolutionary picture which, beginning as a dermatitis, evidenced a tendency to persist and to undergo a succession of clinical and histologic changes toward chronicity which seems to indicate a profound involvement of the entire skin, to say nothing perhaps of the entire individual.

Emphasis on the individual as a predisposing background at first held a relatively small place even in the thinking of the English-speaking group of dermatologists. This was an inevitable result of the process by which dermatology separated itself from general medicine and made

itself, at the start at least, a morphologic specialty. There was an inevitable tendency to emphasize morphologic characteristics and eczema, therefore, became a morphologic designation, clinical in character and with only a shadowy and ill-defined relation to a general medical or individual predisposing background.

Of late, however, British dermatologists have come to issue in the light of the newer knowledge. One now witnesses the splitting off in the one direction of a group represented say by Adamson[1] in recent discussion (reference may be made to recent editorial[1a]), who accepts in the main the German view that the term eczema should be applied to a specific localized sensitivity phenomenon. On the other hand, one sees an equally determined and effective group represented in the utterances of Ingram,[2] who insists that eczema comes into existence and is definable only in terms of the predisposed or constitutionally susceptible individual. In other words, a specific irritant can provoke a dermatitis under certain conditions in everybody, but certain specific irritants are capable only of provoking dermatitis in individuals presenting a definite predisposing background. The first type of dermatitis is dermatitis venenata, or contact dermatitis. The second type of dermatitis is *eczema*.

While the English-speaking point of view has been somewhat tardily developing and accommodating itself to the advances introduced by the German or Continental group, the Continental point of view has been ably represented in the United States by such observers as Wise, Sulzberger, Peck and their coworkers. These observers have been essentially missionaries for the advances introduced by Jadassohn and Bloch into the understanding of specific allergic phenomena with respect to the skin. No reckoning of significant contributions in the English-speaking field would be complete, moreover, without mention of the intensive studies of Coca and his coworkers, and of Rackemann, Rowe, Duke and other observers in the general allergic field, who have applied their general conception to allergic disease of the skin. Of these observers, Coca especially has made important contributions to the constitutional background problem in his analyses of atopy and of the gastro-intestinal phase of allergic etiology. The general importance of the constitutional side has been studied and discussed in resumé in the past by the Finkelstein group of pediatricians, for example; by Rost, who has attempted to analyze and describe the "late exudative eczematid" and the exudative diathesis; by students of the neurogenic and vascular factors such as Kaposi, Pulay, Sack, Brill and Becker; by French observers from Alibert to Darier; and by general clinical observers such as Stokes and his associates.

The contributions of Coca and of Sulzberger, Peck and their coworkers have concerned themselves within the last several years with an improved definition of the various types of allergic manifestations which may present themselves on the skin and in an effort to define (or one might without impropriety say, to theorize on) the identity of the shock structures involved. Coca[3] classifies three common types of allergic skin disease with reference to specific etiologic diagnosis and treatment as follows, the tabular presentation referred to combining his own views with those of Sulzberger and Wise. The first group

includes the *atopic dermatoses* excited by water-soluble antigens, food proteins and inhaled substances. These are tested with aqueous or dried extracts, by intracutaneous, scratch or indirect (Prausnitz-Küstner or passive transfer) methods, show a relatively short reaction time with wheal and erythema, and are to be treated by avoidance if practicable, and if not, by desensitization if possible. The second group includes *contact dermatitis*, which is usually distinguished by its non-familial character, is due to non-antigenic substances, often simple chemicals and vegetable oils, to be tested for by the original material or its extract, using the surface contact or patch test. The reaction time in this group of dermatoses is usually several hours to several days, or even weeks; the reaction is a local, erythematous, and vesicular dermatitis with no production of antibodies, and the treatment is essentially that of avoidance with occasional successful desensitization, especially where vegetable oils are responsible. The last group includes the *fungus dermatitides*, including the eczematous dermatophytids which are the products of hyphomycetes and molds. The test material is the filtrate of broth cultures, the test technique the intracutaneous or patch, the reaction time several hours to several days, and a positive reaction is manifested by an inflammatory papule with eczematous dermatitis without formation of antibodies. Desensitization is considered by these authors as often successful but rather tedious.

Sulzberger, Wise and Wolf[4] have vividly presented in diagram form the current views of their group with reference to the shock structures involved in cutaneous allergic disease. In eczematous reactions, the first group of common allergic dermatoses, the shock tissue is the epidermis; the reaction time, 24 or more hours; the characteristic lesion, spongiosis and intra-epidermal vesicle formation. The causative substances are frequently simple chemicals or products of fungi. Emphasis should be laid in this statement on the spongiosis and intra-epidermal vesicle formation which is accepted by many Continentally trained observers as almost equivalent to a histopathologic diagnostic criterion for "eczema" in the European sense of the term. The second group of common allergic dermatoses, according to these authors, is the tuberculin-trichophyton type of reactions (not infrequently combined with eczematous responses). In this case the shock tissue is the upper cutis or cutis, the reaction time from 24 to 48 or more hours. The characteristic lesion is the lymphocyte and the later epithelioid cell infiltration. The causative substances are usually microörganisms, bacterial or fungus products; the allergic manifestations of this group being then essentially those of "allergy of infection." The test procedure for the tuberculin-trichophyton type of reaction is intracutaneous injection with a reaction time of 48 hours. The third group of common allergic dermatoses, as defined by Sulzberger, Wise and Wolf, are the urticarial reactions. In these the shock tissue is the upper cutis, particularly the bloodvessels, and increasing emphasis is being placed by these authors on the bloodvessels and their relation to blood-borne allergic excitants. The reaction time to intracutaneous, scratch or indirect tests for vascular allergy is from 10 to 30 minutes, the reaction consisting of immediate wheal and flare formation, the characteristic histologic lesion being edema with extravasation of fluid and eosinophils

(wheal). The causative substances for this group of allergic reactions in the skin are foods, inhalants, and the products of microörganisms. The fourth group of common allergic dermatoses is labeled "miscellaneous" and includes drug eruptions, phytids, pyids and other "ids." The shock tissue in these cases is regarded as the deep cutis, epidermis and hair follicles, the reaction time from minutes to days, the lesions multiform in character, including nodules, fixed polychromatic areas, multiform dermatoses and follicular lesions. The histopathology is not specifically defined, the substances responsible include chiefly drugs and microörganisms and the test procedures which are rated as usually inconclusive, include the patch, Moro, or intradermal techniques.

In this summation, then, one has a fairly well-defined picture of the "localist" viewpoint with respect to allergic dermatoses. It will be noticed that at no point does the description cited raise the question of constitutional predisposition, except in the atopic group, as originally described and elaborated by Coca, particularly from the standpoint of the heredity, and the tissue irritability element. Thus far, we believe, it is to be generally conceded that the localists, if one may call them such, have been unable to define what it is that constitutes the irritability, allergic responsiveness, hypersensitivity, or whatever other term may be adopted, which actuates the individual cell of the shock structure in its extraordinary behavior toward what for normal persons are very ordinary contacts.

It is on this point that the attention of those who aim to expand the conception of eczema in the direction of the study of the predispose or eczematous habitus, diathesis, constitution, etc., wish to concentrate their attention. In Ingram's presentation of the constitutionalist viewpoint and in the next two sections of this summary, principal attention is, therefore, given to the factorial interplay in allergic manifestations and to the recognition and study of the predisposing background. Even the most determined localists are coming to recognize that the entire story is not told when the individual reaction has been limited to a shock structure and histologically or clinically defined therein. There still remains an enormous and as yet relatively unexplored field of general medicine and etiology which under various names, as above mentioned, constitutes the stage setting for the crucial act of allergic response, to use one form of metaphor, or the "load" of the human gun which explodes with the "trigger pull" of an allergic excitant.

Factorial Interplay in Allergic Manifestations. One of the most useful conceptions in dealing with analyses of the allergic state is that of multiple etiology. So long as an observer adheres either in his mental evaluations or his experimental attack to a single-cause view of disease phenomena, at least so far as the skin is concerned, he inevitably, sooner or later, finds himself confronted with a hiatus between the results of his theorizing and the effects of his practice. In other words, he clears up his patients temporarily by the removal of what he defines as a causative allergic agent, and then finds them inexplicably and quite inexcusably relapsing with, in a varying proportion of cases, no satisfactory local explanation. He may identify a single allergic excitant or a number of allergic excitants, only to find, following an investigation of the relapse, that the patient now appears to be sensi-

tive not only to the original exciting substance or substances, but to a number of additional substances. In some cases, these substances belong in the general chemical or group category of the originally identified excitants; in others they belong to entirely different groups. In some cases, the patient has clearly lost his sensitivity to what was rated as the original excitant, and developed sensitivities to other excitants which were clearly recognized as negative, or at least as producing no cutaneous response in the original investigation. These paradoxical situations have done more than anything else, perhaps shortsightedly, to discredit allergic study of cutaneous etiology and have given those with limited experience distrust rather than confidence in the ordinary types of allergic work-up or investigation. It is not until a general examination of the entire situation discloses the development within the patient as a whole of new complicating factors or a lighting up of old and previously quiescent ones, that a possible explanation of some of the changing surface allergies comes into existence. To cover this situation, a phrase was developed comparatively early in the study of allergy with respect to the skin and other structures, which is now one of the most useful of all the combinations of words available in this magnificent field in explaining what we cannot explain, or at least in labeling it. This phrase is "broadening the base." (Urbach has recently spoken of parallergy and metallergy.) It is now quite clearly recognized that numerous influences, many of them constitutional both in their general involvement of the body, and in the methods and investigation necessary for their detection, can alter the allergic behavior of the skin. A general or a local infection is capable of bringing into existence, or at least rendering effective allergic predispositions previously completely unrecognized, and perhaps, *ipso facto*, non-existent. Similarly, the dose, so to speak, of an allergic irritant applied to a shock structure seems capable of driving it into frenzy, so to speak, and bringing about an extended or multiple sensitivity which includes *far more than* the allergic response to the original substance or small group of substances first identified by tests or exclusion methods. Bloch, for example, pointed out the ability of the toxic principle of primrose to sensitize all persons in sufficient dosage and to extend the allergic susceptibilities of certain individuals. The state and behavior of the gastro-intestinal tract with reference to digestive ferments, infection, hydrogen-ion concentration, etc., is capable of modifying to a degree highly significant for the skin the production within the tract of allergens and the ease or difficulty with which they are absorbed. A part of the literature on this mechanism is reviewed by Stokes and Pillsbury.[5] Focal infections in other structures, localized infections on the skin with mycotic and pyogenic organisms, are apparently capable of inducing both an extension geographically of skin sensitiveness in involved areas and the development of a general extensive sensitiveness, making possible the clinical phenomena of "ids."

Further notable recent advances in this direction concern the excitation of allergic states by non-allergens, foreign proteins, etc. Among these observations should be mentioned Haxthausen's[6] demonstration that sensitivity to an arsphenamin can be brought about in the human

subject by the parenteral introduction of deazotized horse serum, for example. The increased susceptibility of the atopic and allergically predisposed types of individual to the arsphenamins in intracutaneous tests was demonstrated by Moore, Woo, Robinson and Gay.[7] Sulzberger and Mayer[8] showed that the behavior of guinea pigs with respect to the induction of arsphenamin sensitization varies not only with the season but with the part of the world in which the tests are performed. Striking variations were exhibited between New York and Breslau, apparently not dependent on such influences as diet. Mayer and Cajkovac,[9] from the Breslau Clinic of Jadassohn, showed that the general non-specific sensitivity of the skin in eczematous individuals as well as in those with lichen Vidal and prurigo Hebræ exhibited seasonal variation with peaks in the spring and fall. It is evident, then, that a group of predisposing factors in skin allergic phenomena and sensitivity exists which is not summed up in a description of the site of shock structure or the clinical appearances of the lesions produced by allergic excitants.

In still another field which may be rated as part of the multiple factorial interplay in allergic manifestations, recent advances have been made. This is the demonstration of multiple antigenic factors in seemingly simple and highly specific antigens. Using experimental methods, such as those of Schultz and of Dakin and Dale,[10] Jadassohn and Schaaf[11] have been able to differentiate in bacterial and fungus antigens, including trichophyton and tuberculin, individual antigenic interrelations of a highly complex character. Dakin and Dale, in 1919, pointed out that the crystallin albumen from the egg of the domestic fowl and of the duck behave as distinct antigens for the anaphylactic reactions, the difference between the two being constituted in their physicochemical structure. When the proteins are racemized, the amino acids escaping racemization are not identical in the 2 cases, so that the two albumens, while perhaps clinically [illegible] are in reality allergens of a different order. Jadassohn, [illegible]sch[12] in recent contributions believe that hen egg albumen and duck egg albumen each contains at least two antigens, one of which is identical in the two varieties and the other different. It is apparent, therefore, that etiologic analysis of allergic manifestations is still merely in its crude beginnings and must shortly be carried as far into the field of analytic and synthetic chemistry as the structure and behavior of endocrin hormones.

Another group of factorial interacting influences is the infection-allergic and the infection-contact-irritant interplay. This has thus far been best observed in clinical studies of fungus excited allergies, to which there have been a number of recent contributions. Beerman,[13] for example, in his recent work on leather dermatitis, emphasized the great importance as a sensitizing agent, of the chemicals used in the tanning of leather with respect to susceptibility to fungus infection. Fungus infections may in turn constitute sensitizing agents, rendering the individual reactive to irritants to which he would otherwise be relatively insusceptible. It is hardly to be believed that the mere development of abrasions is the sole explanation of the developed sensitivity, though of course the laying bare of the epidermal shock struc-

ture can logically be regarded as a means of facilitating locally the development of sensitiveness to a particular agent.

Especially may the group of papers concerning themselves with the clinical aspects of arsphenamin dermatitis and its relation to the allergic state, and those describing pityriasis rosea-like exanthems under bismuth treatment[14] be considered as illustrations of the interplay between drug sensitiveness and the fungus infections. Stokes and Kulchar,[15] for example, found that patients with fungus infections, known to be sensitive to arsphenamins flared up at the site of their fungus lesions even under minute amounts of arsphenamin; that some patients with fungus infections were apparently predisposed to arsphenamin dermatitis and that one patient even over a period of some years' observation demonstrated an interrelation between a general allergic state, in which feathers proved to be the excitant of an arsphenamin dermatitis on one occasion, bismuth on another and a fungus infection on a third. The pityriasis rosea-like and extensive "dermatophytid" exanthems now known to be associated with bismuth reactivity are apparently, at least to all clinical appearance, drug excited explosions of cutaneous allergic phenomena and infections. Still another group of interrelations between fungi and non-bacterial allergic excitants has been illustrated by the observations of White and Taub,[16] who showed that fungus intertriginous mycoses of the hands may be predisposed to by contact allergic excitants such as cake flour, for example; and that no lasting recovery can be secured until the presumably protein allergen is excluded from the picture.

Yet another important group of observations illustrating interplay phenomena concerns nickel dermatitis. Cormia and Stewart,[17] for example, observed a case in which a flare-up at sites of nickel dermatitis occurred in association with an extensive dermatophytic outbreak. The especially prolonged association of irritation by nickel in nickel-plating plants with pyogenic infections, though in part a phase of the general relation between susceptibility to dermatitis and pyogenic infections, is well recognized by students of occupational dermatitis.

While perhaps not entirely classifiable with the interplay phenomena, thus far discussed, it is of interest to note here that it is by no means necessary that allergens producing "eczematoid" manifestations shall attack the skin by way of direct contact with the epidermis. Sulzberger and Vaughan's[18] apparent demonstration that inhaled silk particles are capable of giving rise to eczematous silk allergic manifestations in the skin which could not be excited by actual contact has, however, been disputed by Taub and Zakon,[19] who were unable to confirm Sulzberger's observations, possibly through differences in terminologic rating of the cutaneous manifestations. Neurodermatitis, the condition in question with which both observers dealt, is a term frequently of more morphologic than etiologic significance at the present time. Moreover "neurodermitis" when involved in the eczema-asthma-hay fever complex is one of the most involved of cutaneous etiologic problems. It should be noted too that Taub and Zakon did succeed in proving silk responsible entirely for the eczematous or neurodermatitic manifestations in 3 cases out of the 7 they investigated.

Recognition and Study of the Predisposing Background. The foregoing observations on factorial interplay lead inevitably to a discussion of what seems to be the increasing emphasis placed by both clinicians and investigators on the predisposing background of cutaneous allergic manifestations, and particularly of the "eczema" whose definition we discussed at the outset of this résumé. Even the "localists" are beginning to broaden their horizon and deepen their background. Wise and Sulzberger,[20] speaking editorially in their annual review of allergy and immunology in relation to the skin, provide an exceptionally clear example of the evolutionary changes through which the thinking mind is going in the recognition of the broad background of allergic phenomena. Their remarks deserve quotation in their entirety, for they might and in fact have in one form or another been insisted upon repeatedly by "constitutionalists."

"It is recognized that in allergic disease, the so-called 'cause' is not really *the* cause, but simply the 'trigger' (eliciting) factor. So, for example, horse dander is not *the cause* of a patient's asthma. The conditions of constitutional and acquired nature, the conditions which have determined the patient's peculiar susceptibility to sensitization with horse dander—these, plus the dander, are the causes of the asthma. Gerson (in discussion of whose views their editorial appears) attempts to influence the underlying susceptibilities by diet. This is a praiseworthy attempt and an approach not to be neglected. However, in view of our inadequate knowledge of the fundamental mechanisms at the root of the peculiar predisposition to sensitization, such attempts are, in our opinion, at present still doomed to failure in most instances.

"Criticism is doubtless also true in some measure of attempted cures through the finding and elimination of specific allergens. However, the latter method, which is the usual one today, still promises greater chances of success. Nevertheless, the time may not be too far distant when non-specific measures for reducing sensitivity will surpass in efficacy those of specific investigation, elimination and therapy. This is the goal toward which all of us are continually striving.

"The best method for practical application in allergic disease today consists, in our opinion, of a logical combination of all possible non-specific hyposensitization measures, plus all efforts at specific elimination and/or hyposensitization."

Coming from staunch localist spokesmen, this is indeed a concession to the validity of the "constitutionalist" cause, which must draw enthusiastic appreciation from those who have maintained that predisposing background quite as much as, if not more than local exciting cause, defines the entity (if such there be) of "eczema."

In one of the most important practical studies in the American literature, Eller and Schwartz,[21] dealing with occupational dermatitis, have recently emphasized essential elements in the predisposing background of cutaneous sensitiveness. It should be recalled that in so doing, they have followed in the steps of observers such as Bloch, whose breadth of view on allergic phenomena included generous recognition of a predisposing background; and of Mayer, Prosser White, the most distinguished English exponent of occupational cutaneous disease, Gardiner, O'Donovan, and others including Rost and writers

on "diathetic eczema." It must be realized too that as recently as 1932 Downing and Welch,[22] in reviewing the 10-year literature on industrial dermatoses and their treatment, including the standard works of Prosser White and of Oppenheim, as well as Ullmann, Oppenheim and Rille, plus a summary based on a bibliography of 168 titles, practically omitted from discussion the problem of the workers' predisposition to occupational eczema. Eller and Schwartz, on the other hand, accept the broader viewpoint, in part directly and in part by implication, by giving predisposing significance to age, pigmentation, excessive dryness (ichthyosis) and excessive moistness (hyperidrosis, a nervous phenomenon in many cases), focal and local pyogenic infections, trauma, a predisposition to recurrent skin eruptions which they do not attempt to define, and multiply or "polyvalent" sensitivity. This is manifested in the tendency of a worker who has once become sensitive to one substance to become sensitive also to others. They likewise accept fungus infections as standing in the first rank among predisposing causes, together with their phytid sensitization mechanism and its tendency to induce "polyvalent" sensitiveness. They mention heavy metal poisoning as a possible predisposing agent to allergic response still unproven, and finally speak in general terms of the rough, ignorant, careless and slovenly person with poor hygiene who does not keep his skin clean and who is careless about clean clothes. It was a widely overlooked part of the unusual vision of Prosser White and the English group of students of occupational dermatitis that they recognized the age, exhaustion, overwork, worry and seborrheic factors among the predisposing influences in the background of occupational dermatitis—an emphasis which subsequent students of the subject could do well to imitate.

As further evidence of a broadening viewpoint in the literature, Urbach,[23] among observers, who has recently devoted much attention to the gastro-intestinal factors in cutaneous allergy, closes a discussion of the diagnosis and treatment of nutritive allergic dermatoses by urging that "regardless of the method chosen to eliminate the manifestation of food allergy, the underlying causes of the predisposition should also be sought; these may include foci of infection, neglected gastritis or enteritis, hepatic disease, endocrin disorder, etc. If left uncared for, such conditions may later give rise again to allergic processes not necessarily manifested in the skin."[20]

Diet and its collateral implications has had attention among predisposing elements in the writings of Gerson,[24] well known for his contributions to the salt-free dietary treatment of cutaneous tuberculosis; Anderson and Ayres;[25] and from Zitzke and Peters[26] from the standpoint of acid-base equilibrium. The therapeutic side of Gerson's views is given in the discussion of the dietary treatment of cutaneous allergy, but some of his general observations are in point here. Gerson accepted as a factor in his own case an inherited predisposition to furunculosis. He pointed out the relation between infection and allergic predisposition, insisting that infections become chronic through a summation of allergic predispositions and allergizing infections. He maintained that an exaggerated disposition toward inflammation and spasm exists as part of the background of the individual before the disease, and explains

the failure of recovery. Anderson and Ayers, using the specific instance of erythematous lupus of the disseminate type, in which on clinical grounds there is much reason to suspect a profound allergic hypersusceptibility, cited the startling improvement which occurred in a patient under the diet advocated by a food faddist after failure of the usual therapeutic measures. Subsequently the authors tried this same diet in 6 patients with either lupus erythematosus or active dermatitis. Several of the patients were helped, 1 to the extent of 75 to 80%; 2 patients, 1 with a severe actinic dermatitis, remained unchanged. Zitzke and Peters examined the influence of acid-base equilibrium in connection with the treatment of eczema, pointing out the current differences of opinion regarding the influence of acid-base equilibrium and their relation to complex factors in the food intake, including especially mineral salts and the vitamin content, which they feel may explain the seasonal differences in sensitivity of the skin to irritants. In examining the recent literature on acid-base equilibrium in relation to urticaria, Stokes, Kulchar and Pillsbury[27] found in the main that while there might be such a disturbance it was not yet identified in such terms as to be applicable to any large group of clinical cases. Observers such as Criep[28] and Joltrain *et al.*[29] were unable to find any acid-base disturbance in the blood, while Vallery-Radot *et al.*[30] observed low alkali reserve and were able to reproduce urticaria by reproducing the alkali deficiency.

Continuing the discussion of predisposing causes, Wedroff and Dolgoff,[31] approaching the problem of reactive capacity of the skin by way of the use of obligate chemical irritants in eczematous and healthy persons, observed an increased reactivity of the skin in eczematous individuals which they did not consider to be a phenomenon of allergy. They raised the question as to whether this reactivity was to be explained as a constitutional phenomenon which precedes the eczema and plays a rôle in its pathogenesis, or whether it is to be regarded as a consequence of the eczema.

The influence of the nervous system in the predisposing background of allergic manifestations in the skin has received attention mainly from clinicians who have repeatedly observed the apparent neurogenic background of what is technically called neurodermatitis disseminatus and "diathetic eczema"—the eczema phase of the eczema-asthma-hay fever complex. Attempts to reinforce by test procedures the insistence of some observers on the clinically disordered state of the presumably sympathetic portion of the nervous system in these patients have thus far not progressed as they might, largely because of the relatively unsatisfactory methods for determining the function of the autonomic and sympathetic mechanisms and their balance interrelationship. The older literature was extensively reviewed and aligned by Brill[32] in 1926. Recently Marquardt[33] has studied the problem in guinea pigs experimentally sensitized to ursol. Pilocarpin was found to increase the hypersensitivity, but only if it was injected in the latent period preceding the actual development of manifestations. Atropin failed to lessen the hypersensitivity possibly because of the low response of guinea pigs to atropin. The sedative group of drugs had no particular effect in weakening the sensitization except in the case of luminal.

Carrying over his experiments to man, Marquardt tested normal subjects with adrenalin, atropin and pilocarpin and then sensitized them to ursol followed by retesting. The reaction to pilocarpin was definitely heightened by sensitization, while that to adrenalin and atropin underwent no significant change. This suggested heightened response of the vegetative nervous system he believed to be the consequence rather than the cause of the dermatosis, but was obliged to concede that whether the parasympathetic or the sympathetic mechanism responded in the sensitization process, was probably a function of the individual vagus-sympathetic balance in the particular individual under test. This, together with the older observations of Szondi[34] and many others that vagus-sympathetic balance differs from organ to organ and structure to structure, in a given individual, as well as in different individuals, seems pretty well to lay on the shelf for the moment the attempt to approach the problem of vagus-sympathetic background in allergic cutaneous lesions by way of the conventional pharmacologic tests.

One of the most interesting contributions within recent years to the neurogenous background of cutaneous allergic response, and one which if confirmed will almost startlingly affect the whole problem of allergy in general, is the work of Diehl and Heinichen.[35] These authors reported, in 1931, that using the urticarial test wheal, following the intradermal introduction of a known allergen, as the test object, they had been able to influence by suggestion under deep hypnosis the actual local allergic response. In 3 subjects, 2 with bronchial asthma and 1 with sensitization to ascaris, it was possible to produce variations ranging between 21 and 81% by suggesting increase or decrease of the size of the wheal under deep hypnosis in comparison with the previously performed control test. While this work has not yet been extended to allergic cutaneous disease, it urgently needs so to be extended and will go far to demonstrate the influence of the nervous system on the actual phenomena of allergy.

No attempt is made here to review the extensive literature dealing with the neurogenous background of the typically allergic phenomenon of urticaria. For this reference should be had to the summary by Stokes, Kulchar and Pillsbury.

Local Factors in Cutaneous Allergic Reaction. Osborne and Putnam[36] summarized from the extensive literature of both America and the Continent as part of a discussion of industrial dermatoses, certain significant clinical facts which can now be regarded as clinically and experimentally substantiated with regard to the local allergic responses of the skin. It has been shown by Bloch[37] that the allergic state can be brought about by substances of a non-protein as well as of a protein nature. The concentration of the allergy-inducing substance is critically important. By a sufficiently large dose in the case of the primrose allergen, Bloch,[37] as above mentioned, was able to produce an allergic state in the skin of 100% of exposed persons. Allergic reactivity is not necessarily a universal affair involving the entire skin. It may be local rather than general, and limited to a circumscribed area which has been subjected to repeated exposure to the allergen. In industrial dermatitis and in the performance of patch tests, this local

allergic reactivity is particularly important and may be confined to very small areas, comparatively speaking. It is in such cases quite useless to perform tests for sensitivity, particularly patch tests, at points remote from the site of eczematous reaction. In all induced allergic states resulting from contact, there is a refractory period of indefinite length during which sensitization does not occur; but when the sensitization does begin there is always a definite interval elapsing between the contact and the induction of sensitization which is spoken of as the latent period. This latter usually ranges from 7 to 10 days. The Continental group headed by Bloch was unable to demonstrate the presence of antibodies in the blood serum of patients with eczematous eruptions by the passive transfer method of Prausnitz and Küstner, but other observers, such as Ramirez and Eller,[38] have claimed successful passive transfers in some cases. In such cases it is possible that the inhalation route and blood-stream distribution of the allergen claimed by Sulzberger and Vaughan[18] for silk sensitivity applies.

The importance of repeated or prolonged contact in sensitizing previously non-sensitive persons to individual allergens has been especially evident in the field of cosmetic dermatitis. Eller and Schwartz[21] call attention to this feature of industrial dermatitis also and state that such patients do not desensitize, and therefore present an especially difficult problem.

The question of the influence of intermittent *versus* continuous local contact, from the standpoint of sensitizing effect, is recently discussed by Wolter[39] in the case of a lensgrinder who showed allergic reaction as the result of prolonged contact with irritants, but the eruptive manifestations appeared only after he had, for varying periods, avoided actual contact with the eczematogenous agent (in this case, a turpentine substitute). From this illustration is drawn the conclusion that continuous contact tends to immunization or desensitization, while intermittent contact prevents an adequate desensitization. The sensitization appears to persist longer than the desensitization, thus permitting successive intermittent contacts to give rise to allergic eruptive responses which do not occur with continuous contact. Eller and Schwartz[21] have observed this phenomenon in industrial dermatitis and speak of it as "hardening" by continuous contact. This "immunity" or insensitiveness (desensitization?) usually lasts only from 1 week to a month after contact is discontinued, and if work with the eczematogenic substance is then resumed the immunizing process must be repeated. Wise and Sulzberger[40] state editorially that they have repeatedly observed the same phenomenon and that it is a well-recognized factor in the industrial dermatosis of lacquer workers in Japan.

An additional and important feature of local sensitizing mechanisms is not alone the allergen but the conditions under which it gains access to the skin. Eller and Schwartz,[21] for instance, point out that friction not amounting to actual traumatization is an important element in sensitization induction and state that the failure of patch tests to demonstrate local sensitivity is sometimes due not to inactivity on the part of the allergen but to the fact that the patch tests, as applied, fail to simulate the conditions under which the antigen in industrial contact is applied.

A very important element in local sensitization processes concerns

the hydrogen-ion concentration factor. Stauffer,[41] in 1931, showed that substances with a high hydrogen-ion concentration produced a greater reaction than those more nearly neutral. Recently Burkhardt[42] studied more systematically than previous observers the behavior of the skin under alkalinizing influences. The influence of alkalies in the induction of industrial sensitization had been recognized practically but had been attributed largely to the defatting effect of alkali application. Burkhardt, by the development of a test method, showed that the phenomenon is not one of depletion or removal of protective fat or oils, but that there exists a definite group of individuals who are alkali-sensitive. They are deficient in ability to neutralize alkalies applied to the skin, and show dermatitic response under alkalinizing conditions more readily than do normal subjects. Among non-eczematous persons only 8% have a deficient alkali neutralizing power, while in eczematous individuals 90% have a deficient alkali neutralizing power. This is, therefore, a deficiency in physiologic defense rather than a true allergic phenomenon. Removal of sebum and thickening of the keratin layer of the skin are each powerless to modify the effect of this deficiency in alkali neutralizing defense. Inflammatory changes and age influence the alkali neutralizing defense and probably explain a part of the increased susceptibility to eczematous or dermatitic reactions clinically observed in those already the victims of dermatitic processes or in workers during their later years. Burkhardt and his associates postulate carbon dioxid as the alkali neutralizing agent. The difference in reactivity of persons deficient in alkali neutralizing power and those who are normal in this respect was experimentally established through a study of comparative sensitiveness to nickel dermatitis. Thus recognized allergic phenomenon was shown to be directly accentuated by a deficiency in alkali neutralizing defense.

A final very interesting contribution to the study of local skin allergy, as interpreted by skin tests, was made by Rackemann and Simon[43] through the application of controls in the form of 9 standard allergic cutaneous tests to 60 supposedly normal non-allergic individuals. It is indeed surprising to note that this observer found only 30 of the 60 patients to give entirely negative results to the 9 selected allergens (ragweed, horse serum, normal saline, wheat extract, orris powder, silk floss, cat hair, feathers and timothy). Rackemann and Simon conclude that in clinical allergy many positive tests are obtained but few of them are valuable. Evidently if these observations are confirmed it must be conceded that the non-specific zone of cutaneous reactivity to allergens must be extended far beyond the simpler criteria of obligative irritation due to hyperconcentration, particularly of organic chemical agents and metallic salts.

Allergy in Non-eczematous and Non-dermatitic Eruptions. Acneiform responses and papular eruptions tending to simulate acne vulgaris but determined by the ingestion of specific foods have recently been described by White.[44] This author, in a series of 32 cases with recurrent papular and papulopustular eruptions, points out that clinically the process is differentiable from ordinary acne by the absence of comedones and seborrhea and the more or less complete failure of the ordinary treatment for acne, particularly with Roentgen ray. White

quotes Rowe as having observed similar cases. He calls attention to the negligible value of the usual skin tests in determining the incriminated food allergens, and states that the six most common offenders were chocolate, milk, wheat, oranges, tomatoes and nuts. The method of identification was that of elimination diet and the use of non-allergic foods. Skin tests were rated as of little value in these cases.

Urticaria, generally regarded as a manifestation of cutaneous allergic susceptibility, has been examined through clinical study of fairly large groups of cases by Eichenlaub,[45] Menagh,[46] Criep,[28] Hopkins and Kesten,[47] Fink and Gay,[48] Sulzberger and Rostenberg,[49] and Stokes, Kulchar and Pillsbury.[27] Several of these authors summarize a part of the European literature. From these studies the somewhat surprising conclusion seems to appear that chronic urticaria at least is not solely a cutaneous allergic disease in a very large proportion of cases. At least its allergic status cannot be determined satisfactorily by the conventional tests. Patch tests are generally accepted as of no value. Intradermal and scratch tests yield varying proportions of positive results. Eichenlaub rated 40% of his cases as due to food; Hopkins and Kesten apparently found foods of minor importance, for of 200 cases only 4 involved general food allergy, 13 involved the taking of individual specific foods and 15 presented complicated combinations of what seemed to be food sensitivity with other exciting factors such as cold. From the general picture of the background of urticaria afforded by the various studies mentioned, it appears that urticaria is "a disease of complex rather than single causation." Familial predisposition, gastro-intestinal malfunction, gall bladder and biliary tract disease, focal and intercurrent infection, were conspicuous elements. Positive reactions to scratch tests were obtained in 64% of 28 cases in the Stokes, Kulchar and Pillsbury series,[27] but the exclusion of substances to which the patient gave a positive scratch-test reaction and elimination diets were conspicuously unsuccessful as therapeutic measures, at least when used alone. Sulzberger and Rostenberg[49] rate all forms of skin tests as of very little value. Their account of the etiologic background emphasizes drugs as urticariogenic agents, including the salicylates, iodids, bromids, barbiturates, morphin derivatives, phenolphthalein, ipecac, antipyretics and analgesics and arsphenamins. In their opinion the majority of urticarias are not of an atopic nature. Fink and Gay[48] followed 170 cases from 2 to 10 years, finding 15% with an allergic personal history, 28% with a positive family allergic history, 27% negative to skin tests, and most of the positive skin tests obtained to be of problematic significance. They classified their material into etiologic groups, giving the allergic classification a rating of 20%, as compared with 30% attributable to foci of infection, 18% to the psychogenous factor, 5% to the endocrine, and a residue of 25% to undetermined etiology. In the discussion of this paper Vander Veer, Rackemann, Sulzberger, Cohen tended to stress drugs. G. T. Brown emphasized disorders of the gastro-intestinal tract associated with hypoacidity and abnormal intestinal flora which might be interpreted as having some allergic bearings, and added quinin and ipecac to the drug factors. He stated that he had observed sensitization to grass pollen and orris root without hay fever, to be responsible for urticaria.

Gay in closing the discussion stated that eggs, milk and wheat were the chief food offenders, and atophan should be included among the offending drugs.

While purpura and erythema multiforme have been recognized for some time as having in some instances an allergic background, Eyermann[50] has recently reported 18 patients in whom purpura followed the deliberate ingestion of food. Skin tests in 10 patients indicated the offending food in 6. A considerable range of associated allergic manifestations and etiologic foods is described, with egg, milk, wheat, chocolate, beef, potato, oatmeal, string beans and pork leading the list in order of frequency.

Skin Tests. The past several years have seen a curious combination of extension, better differentiation in methods, and greater distrust or more conflicting results in certain methods of skin testing. In general, the tendency has been, so far as dermatologic practice is concerned, toward a decline in the use and acceptance of scratch tests for the recognition of cutaneous allergic states, and a growing emphasis on the patch test of Jadassohn and Bloch, popularized in the United States through the work and writings of Sulzberger, Wise, Peck and others. Jadassohn's original observations on the patch test phenomenon apparently date to 1895, and a full account of the procedure as developed in the clinics of Jadassohn and Bloch is given by Sulzberger and Wise[51] for the American literature in 1931. The immense importance of the patch test for industrial dermatology has been emphasized by Osborne and Putnam,[36] and by Eller and Schwartz,[21] in their extensive studies. It is interesting that Downing and Welch's[22] review of the literature of industrial dermatoses for the 10 years preceding 1932 contains no mention whatever of the recognition of the etiologic agent by patch test, the taking of a careful history and familiarity with the technical processes of various industries and the risks to which workers might be exposed, constituting the larger part of the diagnostic armamentarium.

The literature of the past several years has brought out a number of interesting and important points with reference to the selection of test methods and the value of particular types of test in the detection of allergic phenomena by way of skin or involving the skin as the shock structure. The patch test was regarded by its originators as primarily a test for epidermal sensitiveness, and hence of particular significance in eczema, as defined by European investigators. It was not expected to yield significant returns in urticaria, for example, in which the shock structure is vascular rather than epidermal. As between scratch and intradermal tests, Sulzberger points out that the intradermal test is one for the vascular shock structure and is, therefore, relatively inapplicable to the detection of the etiologic factors in contact dermatitis or eczema. Bloch insisted from the start, however, that the scratch method should likewise be regarded as a test for sensitiveness of the vascular tissues and stated that it was of little if any value in testing for the hypersensitivity underlying the eczemas of adults. Rowe, however, points out that the well-performed scratch test has great value in detecting specific sensitivity to food—a conclusion suggested by Bloch's view that the scratch test is of use in identifying the vascular tissue as the shock structure, influenced by blood-borne (and thus often

food) allergens. That there must be, however, a large factor of individual technical performance and interpretation in skin tests must be evident to anyone who reads the widely varying statements regarding the worth of scratch tests in determining allergic susceptibility in and by way of the skin. Rowe, Schloss, Duke, Rackemann, C. J. White, Urbach, and Peck, in studies of a wide range of allergic phenomena, have called attention to the failure to secure positive scratch reactions in the presence of known hypersensitivities, and to the occurrence of positive reactions which are without etiologic significance. Part of the confusion is due as suggested by Rinkel,[52] to the complexity of the allergic reaction itself, which includes atopic, contact or acquired sensitization, drug and serum sickness, and hypersensitivity induced by infection, more or less indiscriminately under the same terminology in common medical use. Rinkel points out that two types of antibodies are involved, namely, blood reagents and specific fixed cellular antibodies within the shock organs; that allergy within localized groups of cells may or may not be permanent; that skin sensitivity may remain while the shock organ loses its sensitiveness; that sensitivity may precede clinical allergic phenomena as well as remain after they have ceased and that sensitization varies in different areas, and in the same area from time to time. Accordingly, he concludes, and in the main the numerous controversies and exceptions in the literature tend to bear him out, that the decision as to whether or not a patient's symptoms are due to allergy cannot be definitely determined by skin tests. They afford only presumptive evidence which he rates at 50% accurate for food, 85% accurate for inhalants. Only 5% of the consecutive allergic cases studied by Rinkel had complete relief of symptoms from treatment based on their skin reactions alone. Rackemann and Simon's[43] control experiment already mentioned, consisting of skin tests performed on 60 supposedly normal non-allergic patients, tends still further to limit the value of skin testing in the interpretation of allergic etiology. Rowe,[53] among those cited, seems to have the greatest confidence in scratch and intradermal tests, but even he is obliged to recognize the existence of false positives and non-specific reactions. Peck and Salomon,[54] in a thoroughgoing study of 50 cases of eczema in infancy and childhood, dismiss scratch tests as without significance in tracing the etiologic factors in infantile eczema, and go over bag and baggage to the patch test as the effective determinant of etiologic elements in this particular type of eczema.

Among important points to be borne in mind in patch testing technique, the following may be collected from the literature. The concentration of the test substance applied by means of the patch is a matter of considerable importance. For average concentrations not likely to give false positives, reference may be had to standard lists, such as those of Sulzberger,[49] Peck,[55] and Eller and Schwartz.[21] Osborne, Putnam and Saunders[56] especially emphasize this factor and point out that chemical burns are not to be confused with positive patch tests. Danbolt and Burckhardt[57] distinguish in their studies of turpentine dermatitis between the toxic and the eczematous reaction, noting that the latter, which is the significant one, appeared after 24 hours and is best interpreted by the use of weak solutions, the strength being

increased if the results are negative. Patch tests should, as previously noted, be performed at or near the site of the dermatitic or eczematous eruption under study. Following the removal of the patch, Peck[55] states that it is desirable to wait 5 to 10 minutes before attempting to read the reaction. A mild reaction according to this author is to be regarded as significant if it recurs repeatedly. The time during which the patch should be kept in contact with the skin has been gradually lengthened by the observations of various investigators, until it may now reach a period of days or even weeks. The majority of patch tests are, however, read in 24 to 48 hours. Delayed reactions may occur in from 4 to 7 days after removal of the patch and are significant (Peck). Positive tests should be repeated within a month (Peck). A patch test previously performed, resulting in a positive reaction which has subsided, may be observed to flare up upon a repetition of the test at some other and even a quite distant site (nickel—Cormia and Stewart,[17] and arsphenamin). Patch tests performed with high concentrations of chemical allergens or irritants in highly sensitive individuals are capable of producing violent and extensive cutaneous reactions. Caution and experience are, therefore, required in their use.

Important New Groups of Irritants Studied and New Lists. It is proper to remark at the outset of any consideration of this topic that the number of the substances capable of inducing allergic manifestations in the human skin is legion, and grows from week to week and month to month as medical literature rolls from the presses. It is impossible to avoid editorializing on the implications of this flood of reports on allergic reactions to every imaginable substance. Nothing would seem to point more clearly to the belief that something more than a growing complexity of industrial processes and a multiplication of obligative irritants is at the bottom of this extraordinary popularity of contact and other forms of allergy. There is a good deal to suggest both in the hereditary background of allergic manifestations of the atopic type and in consideration of the neurogenous, focal infection, and other influences which set the stage for the allergic drama, that human beings are becoming more sensitive as "total persons," and that allergy is to some as yet unknown extent, a disease of ultracivilization. It is impossible to summarize completely the contributions in the field of new allergens. Several authors, however, among them Weber,[58] Downing and Welch,[22] Eller and Schwartz,[21] Senear[59] (woods), Balyeat[60] (cosmetics) have developed valuable lists, to which reference may be had in attempting to identify responsible substances. To Weber's list of 121 reported plant excitants published in 1930 may be added additional reports by Goldstein[61] of chrysanthemum leaf dermatitis, Rinkel and Balyeat[62] of lettuce dermatitis in a salad maker, cases due to the common weed, tansy (Greenhouse and Sulzberger[63]), the important and widely distributed group of weeds of the genus Helenium (Balyeat, Rinkel and Stemen[64]), tulip bulb dermatitis reported by Horner,[65] hyacinth bulb dermatitis reported by Johnson,[66] and Osborne, Putnam and Saunders' group of plant cases, including sensitivity to forsythia, tulip petals, Boston fern, wandering Jew, and a particular species of coleus. Harville's[67] report deals with a contact eczema from a non-antigenic lipoid substance in the leaf of the bleeding heart.

Ragweed dermatitis has recently come into prominence through the report of Brunsting and Anderson[68] dealing with 18 proven cases due to the oleoresin from the plant. Senear's study of woods remains the most authoritative and complete to date with complete lists and a discussion of the literature. Wood extracts as factors in leather dermatitis are discussed by Berman.[13] In the field of cosmetics, Hoffmann and Peters[69] identified methyl heptin carbonate in a facial cream as the active excitant, and Baer[70] identified the same substances as responsible for lipstick dermatitis. Lash-Lure, reported on several occasions as responsible for severe dermatitis, was recently charged by Forbes and Blake[71] with a death which Wise and Sulzberger analyzed, however, as probably due to intercurrent profound infection for which the dye dermatitis merely paved the way. Kulchar[72] reported contact sensitiveness to the anesthetic "avertin" (tribrom-ethanol) in an anesthetist. Examples of allergic reaction to heat and cold continue to multiply, including the reports of Paul[73] and Levine.[74] Wise and Sulzberger state that urticarial reaction to cold is often a familial disease. Bartels[75] and Richter[76] have recently described excellent examples of heat urticaria. In the latter case, complete cure was obtained by subjecting the patient to slight degrees of heat with gradual increase, In addition to the general cataloguing of sensitivity to chemicals, attention should be drawn particularly to nickel dermatitis, for nickel is so universally a factor in everyday life, that sensitivity to it has real significance for the ordinary case, especially in dermatitis involving the spectacle contact areas of the face ("white gold" contains nickel), and eczema of the hands. The characteristics of this, perhaps the only metal sensitization thus far recognized, have been studied in this country by Goldman,[77] Fox,[78] and particularly by Cormia and Stewart.[17] The latter investigators conclude that while in man the phenomenon is generally allergic (Burckhardt also) it cannot be induced as a true allergic state in the guinea pig. Among other chemical irritants, Osborne, Putnam and Saunders[56] emphasize the importance of soaps and the sulphonated oils used in their preparation. Van Vonno *et al.*[79] have pointed out that in 28 cases of bakers' eczema, a part at least of the sensitivity is not to the wheat, but to the ammonium persulphate frequently present in the flour. The importance of the careful and detailed analysis of complex food products, occupational irritants, etc., is emphasized and even ingested anilin dyes have been incriminated by Baer[80] when used as coloring matter in foods.

A number of special allergy-inducing agents have had intensive study recently. Among them should be included silk, rubber, leather and rhus, or ivy poisoning.

Silk. Growing interest is manifested in the relationship of silk sensitivity to atopic eczema (neurodermatitis disseminata). Figley and Parkhurst[81] have recently reported 5 cases of atopic eczema in which the major sensitivity was due to silk, and in which the reagin could be demonstrated. All 5 patients had other manifestations of atopy, involving the respiratory tract, and all but 1 reacted to other inhalants besides silk. The authors believe that in atopic eczema silk exerts its effect as an inhalant rather than as a contactant. The authors indeed believe that inhalants play as great or perhaps a greater

rôle than ingestants, in the complex etiologic background of atopic eczema, and quote the case of Rattner and Pusey,[82] in which a neurodermatitis in a young man was definitely proved to be due to the perfume used by his wife. Sulzberger and Vaughan[18] also subscribe to this point of view, and believe that inhalants and the respiratory route of absorption deserve further study in the pathogenesis of atopic dermatitis, urticaria, and some forms of infantile eczema. They feel that allergen-free rooms are just as essential as elimination diets in the treatment of these problems. They have furthermore experimentally proved the inhalation of allergens, such as silk in particular, can cause a definite exacerbation of atopic eczema; and conclude that the elimination of, or hyposensitization with inhalant substances combined with the elimination of, or hyposensitization with food allergens is necessary before reaching the conclusion that a positive skin test is of no clinical significance in atopic dermatoses. Taub and Zakon[19] have not been able to confirm Sulzberger's observations that nearly all patients with atopic dermatitis give a strong reaction to silk, and show the reagins to this substance. The authors have made several thousand tests with silk proteins in hay fever, asthma and various dermatoses, with such a large percentage of negative results that they conclude that Sulzberger's silk protein may have been at fault or contained histamin. It is noteworthy, however, that in the detailed histories of 7 patients on whom they reported 3 cases were shown to be definitely sensitive to silk, and responded beneficially to its complete elimination from the environment. Furthermore, Taub,[83] in 1930, reported 105 reactions to silk from the practices of 60 allergists. Its etiologic significance was proved in 27 patients, 22 of whom had eczema, 4 urticaria and 1 asthma. From these papers we can conclude that silk is definitely to be reckoned with in the investigation of patients with atopic eczema, even though its instrumentality may be proved in a relatively small proportion of patients. Nevertheless, the recognition of its influence is of distinct aid in the evaluation of a problem which hitherto has yielded such comparatively poor therapeutic results.

Rubber. While the dermatitis produced by contact with the chemical substances used in the manufacture of ordinary rubber goods has been long recognized, it is not generally known that the finished products such as rubber gloves or condoms may give rise to contact eczema. In a detailed case of a physician who developed a vesicular eczema following the use of both rubber gloves and condom, Obermayer[84] reviews the chemistry of the manufacture of rubber, and enumerates the substances which are eczematogenic. In the particular patient under discussion, the instrumentality of crude rubber, the chemical substances employed in the manufacturing of ordinary rubber goods and ordinary rubber goods themselves were eliminated, and it was assumed that the irritating agents were formed during the process of cold cure vulcanization. Schwartz and Tulipan[85] review an outbreak of dermatitis that occurred among 8 workers in the manufacture of sheet rubber goods. The new rubber products contained three accelerators and an antioxidant. Four of the 5 patients investigated by patch testing reacted to accelerator A, which consisted essentially of tetramethylthiuram disulphid. One patient was sensitive to all the accelerators, as well as to the anti-

oxidant. Accelerator A has been previously implicated as a cause of dermatitis by Kindel and Hayhurst.[86] Obermayer enumerates all of the accelerators which have been reported to be the cause of dermatitis. All are of complex chemical nature, such as hexylmethylenetetramin, which commonly produces a dermatitis known as "rubber itch." This accelerator is responsible for so much trouble that its use is being discontinued according to Eller and Schwartz. Sulphur is also used extensively in the manufacture of rubber and consequently this substance and its derivatives must be taken into consideration in any attempts to determine the etiologic agent in the production of a dermatitis due to rubber. The recent report of Rattner[87] on sensitization to a rubber condom leads one to believe that rubber sensitivity is probably more common than recognized, and apart from the rubber industry, leads to an investigation of the possible instrumentality of rubber, especially in the form of gloves among physicians, housewives and other occupations requiring protection of the hands. Dermatitis of the eyelids traced to the rubber covering of eyelash curlers has even been reported. An interesting review of eyelid contact dermatitis was made by Hollander and Baer.[88]

Leather. Beerman[13] has reviewed the factors involved in the production of leather dermatitis with particular reference to that induced by contact with leather hatbands. The relatively low incidence of dermatitis due to leather suggests the prominent rôle played by individual susceptibility and the influence of the predisposed background. It is interesting to note that cases have been reported from shoe leather, leather wrist-watch bands, leather jackets and leather gloves, as well as a predominant number of cases from contact with the hat band. As would be anticipated, the manufacture of leather is highly complex, involving preliminary preparation of the hides, tanning with vegetable tannic acids, quebracho extract, sumac and chestnut as well as synthetic tanstuffs manufactured from phenol and hydrocarbons. Subsequently, the leather is subjected to treatment by various dyes, finishes and binders. The author was able to trace one of his cases to sensitization to the synthetic tanstuff and another to the vat dye. The author has investigated and illustrates by cases the interplay of the multiple factorial background of leather dermatitis, and believes that fungus infections probably predispose to leather dermatitis through polyvalent broadening of the sensitivity. Conversely an allergic (leather) dermatitis may predispose to or reactivate a fungus infection as has been investigated and elaborated by White and Taub.[16]

Ivy (Rhus). Although the instrumentality of plants in the production of a sensitization dermatitis has been discussed above, special attention is directed to ivy because of the ubiquity of the plant and the high percentage of persons who are susceptible to it. Spain, Coca and MacNair[89] have shown that 60% of persons react to poison ivy, this figure only being exceeded by the 80% who are allergic to Ascaris. Gowen[90] has recently reviewed the prevention and treatment of Rhus toxicodendron poisoning and elaborates in detail the various methods of treatment which he has found successful. A unique method of immunization has been proposed by Maisel,[91] who advocates the direct application of gradually increasing doses of an extract of poison ivy by means of the daily bath.

Treatment and Recovery Factors. The treatment and recovery factors involved in the allergic dermatoses furnish problems of extraordinary complexity. From the controversial cross-currents of the literature of the last several years, the possibilities and impracticalities of a number of modes of treatment can easily be recognized. Withdrawal of the offending allergen, the logical mode of attack, is confined in its usefulness to comparatively simple problems in which one or two contact agents can be eliminated either by removing the worker lastingly from his contacts or displacing the offending substance in the industry. In everyday life, however, it is increasingly evident that sensitivity is at least as often if not more often polyvalent than monovalent, and one confronts therefore the necessity for removing the patient from a series of contacts which may hamstring him in the ordinary conduct of life. The disconcerting trick of an individual allergen, particularly one involving an infectious agent, of "broadening the base" or inducing polyvalence against the patient's constitutional background or allergic habitus, still further complicates the situation. In the most discouraging example of cutaneous multiple sensitivity, namely, the so-called neurodermatitis disseminata (synonymous for many with the eczema phase of the eczema-asthma-hay fever complex and with the exudative diathesis and "diathetic" eczema), careful observers, as for example Sulzberger and Rostenberg,[49] have finally yielded to the clinical practicalities in the case and have recognized that little short of life under a continuous process of elimination diet and incarceration in allergen-free rooms is possible for the atopic type of individual if the therapeutic problem is approached solely from the allergen elimination side. The impossibility of the situation was earlier pointed out by Stokes[92] in a discussion of the treatment of diathetic eczema. Sulzberger and Rostenberg voiced the clinical experience of a number of dermatologists and allergists that many strongly positive reactions in the atopic individual are not necessarily of etiologic significance in his eczema or neurodermatitis, and this, with their polysensitivity, reduces the therapeutic problem *ad absurdum*.

Granted then that when the number of allergens is sufficiently small and that they are individually removable from the patient's everyday life, the results may be highly satisfactory, the next question is raised when such antigens must or will be restored to contact with the patient. This concerns the possibilities of desensitization. Here again, conflict of opinion is notable. In the first place the mechanism of sensitization is not as yet clearly understood even in its local manifestations in contact dermatitis. Aside from the factorial interplay previously discussed, the actual phenomenon is involved in problems of "silent" sensitization (Bloch, quoted by Beerman[13]) and by the problems of a refractory, a latent, and a reaction period (Sulzberger and Wise[93]), which may range individually and collectively from hours to years under influences which are by no means defined as yet. Opinion on the possibilities of desensitization is pessimistic. While it is widely assumed that continuous or frequent contact with high concentration tends to sensitize, the observations of Eller and Schwartz[21] on industrial dermatitis lead them to the belief that it is continuous contact with a local allergen which results in a measure of desensitization sufficient

to enable the worker to "harden" to the requirements of the industry. Similarly one finds Wolter,[39] above quoted, presenting a case to illustrate the effect of intermittent rather than continuous contact in producing local sensitization. Frühwald's[94] questionnaire quotes Haxthausen, Kranz, Mayr, Urbach and Vohwinkel and Schmidt as rating desensitization procedures as unsatisfactory. Sulzberger and Wise[95] editorially limit the practical use of specific hyposensitization to dermatoses produced by certain oils and secondary fungus eruptions, but speak hopefully of the future. In view of the general differences of opinion as to mechanism and results in the entire field of desensitization, it is not surprising to see experienced observers such as Osborne, Putnam and Rickloff[96] in disagreement with Sulzberger and Wise[97] as to the therapeutic possibilities and value of desensitization procedures in the field of fungus-excited eczema and dermatitis. Even the latter found that while desensitization could be accomplished with trichophytin in 15 out of 18 highly coöperative patients, its value as a lasting protective procedure was questionable and uncertain. Even in the field of vegetable oil dermatitis, Gowen[90] found that all the available methods of desensitization, against Rhus ranging from chewing of the leaves to daily baths (see also Maisel,[91] above) and intramuscular injection of the almond oil extract conferred an immunity ranging only from 1 to 2 years. Evidently, then, the problem of desensitization as a therapeutic technique does not reach its all-time low in the atopic constitution alone, but is a method of questionable usefulness in all fields of cutaneous sensitivity.

The problem of the influencing of the allergic state with reference to the skin by dietary measures is receiving increasing attention, and with it, as may be expected, some paradoxical and conflicting experiences. Within this field one observes as in other problems in allergy a "specifist" group and a "non-specifist" group of opinions. To the specifists belong the efforts to recognize and treat underlying allergic factors by elimination diet (Rowe, C. J. White, for example). Many students of infantile eczema, especially among pediatricians, lay emphasis on the importance of food exclusions in the control of the eczemas and eczematoid dermatitides of infancy, and it seems probable that during this relatively uncomplicated stage of the development of the human being, the simpler types of food sensitivity and the elimination of specific food allergens reach their greatest effectiveness. On the other hand, in the critical study of egg-white sensitization, seemingly one of the most direct and simple of food allergies involving a cutaneous shock tissue, Woringer[98] on the one side contends for the importance of allergy to egg-white in the eczemas of infancy, while Sallenbach,[99] Peck and Salomon,[54] Nitschke,[100] Hill and Sulzberger[101] point out from various angles the inconsistencies upon which this earlier opinion is based, and the probable relative unimportance of egg-white sensitization as determined by cutaneous tests in the diet-induced eczemas of human beings. This illustration at least furnishes abundant discussion material for the atopic and the non-specific background of what were formerly rated as specific cutaneous allergic phenomena.

Urbach,[23] in his recommendations for the general management of nutritive allergic dermatoses, points out that proteins are the most frequent offenders but that carbohydrates, fats, salts, acids, spices

and etheric oils may function as such. Pronounced distaste for a certain food is an important symptom. An overdose of the food in question may establish the relation. The only diet which Urbach concedes to be practically free of nutritive allergens is one of pure sugar, of which he gives 300 gm. per day in a weak tea for a 2-day period with the patient in bed. The usual successive single or simple food additions are made to this non-allergic diet, at 24-hour intervals, proteins being first employed, followed by carbohydrates, fats and the other above-named food elements in successive groups. Urbach recommends as a means of saving time the use of "propeptans," taken ¾ hour before the meal at which the foods will be ingested. If the ingested propeptan protects the individual against the particular food ingested, improvement occurs within 3 days and successive elimination of the propeptans used serves to identify the particular propeptan which is protecting the patient and which corresponds to the protein that acts as his allergen. Desensitization to the recognized allergen may follow the use of graded but exceedingly small doses of the incriminated substance, these doses being of the order of 1 drop of egg-white to ¼ liter of water at the start. The complexity of these methods is evident in the description and as in the case of the Rowe elimination diet will make their practical applicability under the home conditions of most patients very difficult. This is a general criticism of attempts to deal with polyvalent food sensitivities, so that between the uncertainties and at times non-specificity of cutaneous tests for food allergens and the complexities of elimination dieting, the average patient is apt to be limited to an exclusion of the principal offenders as detected by skin tests, plus those indicated by an inquiry into food dislikes and clear-cut food upsets and gastro-intestinal reactions.

Gerson,[24] whose contributions to the salt-free dietary treatment of cutaneous tuberculosis are well known, takes, in part on the basis of personal experience, an exceptionally broad view of the many mechanisms involved in persons presenting what appear to be nutritive allergic manifestations. He points to the fact that not only must the specific allergen be eliminated, but that attention must be given to defective detoxicating power of the liver, its effective capacity for forming antibodies, pathologic modes of splitting up the protein molecules, heightened permeability of vessel walls and altered reactivity in a changed nervous system. He emphasizes that the totality of the allergic constitution must be taken into account. This article, exceptional in its breadth of viewpoint with respect to the complex mechanism of allergic phenomena should be read in its entirety. Gerson points out that the withdrawal of a single antigenic substance may alter the balance between non-specific and specific factors in a way to bring about recovery even though other elements may be completely overlooked. Patients from whom salt has been long withheld will become more sensitive to Roentgen rays and aspirin and less susceptible to infections. His particular formula for the dietary study and treatment of patients in whom this portal of entry of allergens is suspected includes an extremely low salt intake, no animal protein in the first 5 to 7 weeks, exclusion of muscle meat and meat soups, milk, eggs, fish and legumes, a low intake of carbohydrate and a high intake of fluid. The diet is

purposely made exceptionally rich in potassium, calcium and vitamins, and moderately rich in fats. Spices, condiments, tea, coffee and coffee substitutes, chocolate, cocoa, alcohol and tobacco are forbidden because of their irritative effects on the vegetative nervous system, which prepare the way for allergens to take effect. For a régime of this sort, Gerson claims a slow but definite desensitization which the author rates as non-specific in character. Gerson apparently observed the homologue of the situation described by Wolter in which certain specific responses to antigens do not appear until the general allergic state improves through the elimination of the larger part of the incriminated antigenic substances.

Among other more or less non-specific desensitizing measures, using the alimentary tract, one may note the now more or less familiar employment of hydrochloric acid by mouth, based on the fact that a considerable proportion of allergics exhibit hypochlorhydria (alluded to by Brown[48]); high vitamin intake, especially of A and B, referred to by White[44] and Redaelli,[102] and skeptophylaxis. Comel[103] felt that vitamin D, through its effect on calcium metabolism and fixation favorably influenced eczema in general. In connection with the attempt to use vitamin B carriers in the treatment of eczema, sensitivity to wheat must be borne in mind and also sensitivity to yeast as recently described by Biederman.[104] Skeptophylaxis, alluded to by White[44] and Urbach[23] consists in a species of Bezredka or antianaphylactic effect obtained through the gastro-intestinal tract by administering a minute amount of the suspected food $\frac{3}{4}$ hour before the taking of larger quantities as part of the meal. This has a definite immediate protective effect, and if persisted in, is rated by Urbach as a valuable method of permanent desensitization.

Preventive Measures in Industrial Dermatitis. The increasing responsibility placed on or assumed by industrial concerns for the occurrence of industrial contact dermatitis in their employees makes particularly important the recommendations of Downing and Welch[22] and Eller and Schwartz,[21] based on a review of the literature and experience regarding preventive technique. The former authors emphasize easy and accessible consultation with the plant chemist, the maintenance of the workmen in a state of physical and mental well-being, frequent inspection of the employees with immediate removal of those reacting to an irritant, and attention to the hygienic conditions of the place of employment. Informal discussion of industrial dermatoses within the Reviewers' knowledge too often brings out a disposition to secrecy and non-coöperativeness on the part of manufacturing and industrial interests which can only react to their own disadvantage. Eller and Schwartz in great detail point out that many processes involving injurious chemicals can be totally enclosed, the raw materials being sucked up into reservoirs from which they flow into retorts and tanks, merely by the turning of a valve. The finished products may be barreled without the worker's having come in contact with any of the intermediates of the manufacturing process. The worker may in some cases be protected against irritating substances by wearing suitable protective clothing such as rubber gloves, aprons, masks and goggles, and

by the application of protective ointment such as has been described by James.[105] The actual elimination of unessential, strongly eczematogenous chemicals is being carried out. It is important that new workers be carefully examined before being received into an industry for evidence of predisposition, especially where the dermatitic hazard is high. In the factories where synthetic dyes and complex organic compounds are manufactured, new applicants should be patch-tested to the chemicals with which they will be called upon to work, and those found to be hypersensitive rejected. There should be periodic routine examinations of the workers in search of those who have skin and other ailments (especially skin infections J.H.S., V.C.G.) and these should have prompt attention.

Eller and Schwartz emphasize the importance of proper ventilation of work-rooms. If the irritating gas or dust is sucked away from workers there will be fewer cases of dermatitis. Exhaust hoods should be placed over processes giving rise to irritating dusts or gases. Floors should be washed at the end of each shift to remove dust. Cleanliness should be emphasized. Shower baths and lockers should be provided, and their use should be obligatory; work-clothing should not be worn to the street or for everyday purposes; the furnishing of clean work-clothes may prove an actual economy. This is particularly true where oils are used in industrial processes, and helps greatly to prevent oil furunculoses and acne.

The legislation involved at the present time is not uniform in different states, and model compensation laws should be drafted after proper study. The use of expert testimony is subject to many abuses, and for that reason it is particularly recommended by Eller and Schwartz that compensation boards be composed of or guided by the opinions of an impartial group of state-paid physicians, totally divorced if possible from politics, and chosen for their familiarity with industrial processes and industrial diseases. Physicians obliged to deal with industrial cases should be made familiar with the compensation laws of their own state, together with the more important decisions of the higher courts.

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PHYSIOLOGY

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Chemotropism of Leukocytes in Relation to Their Rate of Locomotion.—H. M. Dixon and M. McCutcheon (Laboratory of Pathology, University of Pennsylvania). By chemotropism of leukocytes is understood a directional response on the part of the cells, which move toward

a source of attraction (if the response be positive), instead of moving at random, as is the case in the absence of an attracting body. Whether a leukocyte reacting chemotropically travels faster than one moving at random, that is, whether chemotropism has not only a directional but also a velocity component, appears not to have been decided. In order to answer this question, experiments were made *in vitro* with human neutrophils. Leukocytes were observed with the microscope and, with the help of a drawing ocular, their paths were recorded on paper. From these records the rate of locomotion was computed, first, for leukocytes moving toward bacteria (or other attracting bodies) in the same microscope field, second, for leukocytes moving in parts of the same preparation so far distant from bacteria that their locomotion was at random. The sources of attraction used were S. aureus, S. albus and collodion particles (of about the size of bacteria). Leukocytes in the vicinity of each of these kinds of particles were strongly attracted by them, but their rate of locomotion was no greater than that of cells moving at random. For example, the mean rate of locomotion of leukocytes moving toward collodion particles was 35 microns per minute; for cells moving at random the rate was the same. It is concluded that the chemotropic response does not involve increase in rate of locomotion.

A Critical Study of the Sullivan Method for the Determination of Cystin.—James C. Andrews and Kathleen C. Andrews (Laboratory of Physiological Chemistry, University of Pennsylvania). The cause of the increase in apparent cystin content of aging cystinuric urines, as determined by the Sullivan method for cystin, has been traced to atmospheric oxidation of certain urinary constituents which markedly inhibit the formation of color in the Sullivan method. These constituents are, as a rule, substances with strong reducing properties. Ascorbic acid (vitamin C) is one of these constituents but is responsible for only a comparatively small proportion of this inhibiting effect on the development of color in the Sullivan method. A further search is, therefore, being made to determine the identity of these other urinary constituents. While they inhibit color formation in the Sullivan method they do not reduce dichlorophenol indophenol as does ascorbic acid. The original hypothesis of Brand and coworkers, who postulated that part of the cystin excreted by the cystinuric is in the form of an easily decomposed complex, must therefore be discarded.

Examination of a large variety of compounds to determine their ability to inhibit the formation of color from constant amounts of cystin has yielded the following results. The most effective inhibitors are such reducing agents as ascorbic acid, adrenalin, hydroquinone, pyrogallol, diamidophenol (photographic developers in general) and tannic acid. Hydrogen sulphid and certain cyclic derivatives of cystin (such as cystin hydantoin), which readily produce soluble sulphids under the conditions of the Sullivan method, are equally effective. It is obvious, therefore, that the lower results for cystin given by the Sullivan method, as compared with other methods, and which have been attributed entirely to its greater specificity, may often be due to

its failure to produce a proportionate amount of color in the presence of these inhibitors.

A further class of substances, while effective only in larger amounts, are capable of producing erroneous results in the determination of cystin. These include the simple aldehyds, the sugars (both mono- and disaccharids) and various sugar derivatives such as glycuronic acid, its lactone and certain of its conjugation products.

The observations of Lugg and of Rossouw and Wilken-Jorden concerning the interference with the Sullivan method of certain amino acids when present in large amounts are confirmed. These effects, however, are negligible compared to those mentioned above.

The inhibition curves of adrenalin and ascorbic acid form the basis of a satisfactory method of determining these substances in the absence of other such inhibitors.

Factors Concerned in the Measurement of Serum Volume.—F. WILLIAM SUNDERMAN and J. H. AUSTIN (Laboratory of Research Medicine, University of Pennsylvania). The studies demonstrate a marked change in the color values of vital red dissolved in aqueous solutions of salts of different ionic strength and ion species, with further alteration in the presence of serum.

A technique of colorimetry has been developed in which two standards are prepared by adding dye to serum obtained from the subject before injection of dye, one standard weaker than the weakest unknown, and the other standard stronger than the strongest unknown. The standards are compared in a colorimeter against a neutral tint filter, giving an optical density of 1 and a No. 75 Wratten filter in the lens system. A straight line drawn through the reciprocals of these readings furnish a valid basis for interpolation of reciprocals of the unknowns similarly read, and from this may be determined the concentration of dye in these unknowns.

A method of using the benzidin reaction has been developed for the purpose of detecting the presence of hemoglobin in serum containing vital red.

The Reactions of Hypophysectomized Rabbits to Epinephrin.—C. BACHMAN and G. TOBY (Laboratory of Biochemistry, McGill University).

Addendum.

In regard to a reference in Dr. Dameshek's article (AM. J. MED. SCI., 190, 617, 1935) to Seyfarth's introduction of sternal puncture, Dr. D. N. Banerjee, of Calcutta, writes us: "The value of puncture of the sternum in the diagnosis of kala-azar was announced by me prior to Seyfarth as long ago as April, 1932 (*sic*) in the Calcutta Medical Journal (vol. 16, No. 10, p. 400) and abstracted by C. M. Wenyon in the Tropical Diseases Bulletin (vol. 20, No. 2, p. 97, 1923). The abstract runs thus: 'Banerjee (Dhirendra Nath) An Announcement. A Preliminary Note on the Diagnosis of Kala-azar by Examination of Bone-marrow—reprinted from Calcutta Med. Jour. (vol. 16, No. 10, p. 1, 1922). The author announces what he regards as a simple and safe method of examining for leishmania in cases of suspected kala-azar by obtaining marrow from the sternum. The anterior plate of the gladiolar portion

of the sternum is opened by means of a Southey's trochar and material obtained from within the bone by means of a hypodermic syringe. He has obtained parasites from all the cases of kala-azar he has examined. A full report of the results of his investigations will be published later. C. M. W.'" Dr. Dameshek has made the following comment: "Seyfarth in his original communication (Deutsch. med. Wchnschr., 49, 180, 1923) states that he was led to use the sternal biopsy while working at a hospital for tropical diseases situated on the Ægean Sea. He was there in 1916 and 1917 and found the method of value in the diagnosis of malaria and kala-azar, since splenic puncture was often a dangerous method. . . . If Banerjee's statement is correct, it deserves some notice in the accessible medical literature."

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ORIGINAL ARTICLES.

TREATMENT OF PERNICIOUS ANEMIA WITH INTRAMUSCULAR INJECTIONS OF A HIGHLY CONCENTRATED SOLUTION OF LIVER EXTRACT.

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(From the Medical Clinic of the Peter Bent Brigham Hospital.)

This report deals with the results observed in the treatment of 33 patients with pernicious anemia by means of intramuscular injections of a highly concentrated and refined extract of liver. The extract, so concentrated that 1 cc. contains the active principle derived from 100 gm. of liver, was prepared by Dr. Guy W. Clark, of the Lederle Laboratories, and was supplied for the purposes of this study as early as July, 1934.

Of the patients to be considered, 28 first received treatment when their red blood cell levels were below 3,500,000, having received no liver treatment for at least several months previously. In the majority no previous liver treatment had been used at any time. It has been possible to observe 26 of these patients under treatment with the same liver extract during periods varying in duration up to 1 year after their red blood cell levels had reached or passed 4,500,000 in order that their maintenance requirements might be determined.

In addition to the 28 patients in whom treatment was begun during relapse, 5 others have received injections of the 1 cc. material for slightly more than 1 year. The 5 patients were selected because each had been previously maintained on intramuscular injections of 3 cc. (Lederle) of liver extract prepared from 100 gm. of liver

for from 1 to 2 years during which time their maintenance requirement was found to be somewhat greater than that of the average of the patients under observation, as previously reported. It was believed that such a selection of patients would favor a more critical test of the efficiency of the new material.

Potency of the 1 cc. extract was demonstrated in 25 of the 28 patients treated during relapse by means of reticulocyte counts made daily on all patients in so far as it was possible. Ten of the patients were not admitted to the hospital for treatment and it was not always feasible to have them return daily for observation. The reticulocytes were counted in dry blood film preparations made on coverslips coated with a dry film of 0.5% alcoholic solution of cresyl blue as used in previous studies.[1] The effective or erythrocyte-producing potency of the extract was demonstrated, as previously advised,[2,3] by observation of erythrocyte production during a period usually of 4 weeks following the institution of therapy during relapse and by determination of the required amount of liver extract to maintain the blood in normal condition during sufficiently long periods of time to serve such a purpose. Periods of ½ year or longer are considered preferable for this purpose. Of the 28 patients first treated during relapse, 16 have been followed for from ½ to 1 year from the time the red blood cell levels had reached 4,500,000 and, therefore, serve as satisfactory cases to demonstrate the maintenance requirements along with the 5 cases reported only for that purpose.

Results of Treatment During Relapse. In Table 1 are recorded data obtained in 28 patients first treated during relapse. In those patients in whom blood studies included reticulocyte counts the highest count is recorded together with the day following the onset of therapy upon which this was observed. The magnitude of the reticulocyte response has varied considerably in the blood of the individuals of the groups classified according to the various initial erythrocyte levels, as is to be anticipated from previously reported observations.[2] Although the amount of liver extract injected for treatment during relapse and the method of its use has varied considerably in this group, it is obvious that this has had little influence upon the magnitude of the reticulocyte rise, although it has influenced the rate of their production.

Erythrocyte production was slower during the first 2 weeks of treatment in the 3 patients treated with small daily doses than it was in those receiving larger initial doses, whereas those receiving minimal amounts of material (2 cc.) during the first 4 weeks tended to produce erythrocytes less rapidly toward the end of this period than did those who received a greater amount of material, regardless of whether or not the material was given in daily small doses or larger less frequent ones.

The rate of erythrocyte production observed in this group com-

pares favorably with that previously reported[2] in a group of patients treated with the 3 cc. material derived from comparable amounts of liver, that is, from 400 to 700 gm. during the first month. That the actual rate of erythrocyte production is slower in many of

TABLE 1.—DATA OBTAINED DURING THE FIRST 4 WEEKS OF TREATMENT OF 28 PATIENTS WITH INTRAMUSCULAR INJECTIONS OF A CONCENTRATED LIVER EXTRACT.

Case No.	Peak of "retic" rise. %	Day of "retic" peak.	Initial R.B.C. level in millions per c.mm.	Daily R.B.C. increase in thousands during 4 weeks.				Amount of extract injected, in cc.*	Day given.
				1st.	2d.	3d.	4th.		
1	32.1	5	1.08	146	150	...	116	4	0
2	23.1	4	1.13	63	108	68	65	4	0
3	34.1	5	1.15	130	123	99	83	1	0–12
4	21.0	5	1.27	104	160	...	94	1	1–9–12
5	18.6	5	1.58	90	102	90	88	2	15–21–23
6	16.2	4	1.60	83	96	105	99	1	0–1
7	28.8	6	1.67	230	116	133	108	2	25
8	30.2	4	1.67	83	106	...	...	2	0–1
9	17.7	5	1.79	97	103	85	75	1	0–1
10	10.2	6	2.02	72	...	...	85	1	0
11	8.0	6	2.03	124	78	87	74	1	0–19
12		...	2.08	146	78	58	61	2	0–10
13		...	2.18	143	...	...	53	1	18–25
14	11.5	4	2.36	...	108	...	...	2	0
15	21.9	7	2.36	146	110	96	81	1	0–1
16	4.7	6	2.43	67	70	70	77	4	15
17†	24.6	9	2.04	64	69	87	...	2	0–8–18
18†	13.1	6	2.46	66	97	71	73	1	0–1
19	5.0	6	2.57	...	51	39	40	1	7–14–21
20	7.6	6	2.63	76	116	120	...	0.14	0–10–18
21	19.9	4	2.73	54	89	80	104	0.1	Daily for 28 days
22	7.2	5	2.82	114	116	...	63	1	Daily for 28 days
23	7.8	5	2.84	107	96	96	63	2	0–6–13–20
24	10.4	5	3.00	113	105	73	75	1	0–1
25†	13.5	7	2.69	0	43	28	55	2	0–1
26		...	3.01	80	83	47	53	1	12
27	2.9	5	3.23	0	47	60	60	0.1	Daily for 28 days
28	5.1	7	3.36	6	69	70	56	2	0–1
								1	0–1
								2	7–14–21
								1	0–2
								2	13
								1	0–1
								2	7–14–21
								1	

* 1 cc. = 1 vial derived from 100 gm. of liver (Lederle Laboratories, Inc.).
† Extract administered in small daily dosage for 28 days.

this group than the averages previously reported is no doubt due to the fact that they received, during the first 4 weeks, extract derived from smaller quantities of liver, that is, from 200 to 400 gm. However, the average daily erythrocyte increase during 28 days for the 9 patients whose initial erythrocyte levels were below 2,000,000 (see Table 1) was approximately 92,000, as compared with 98,000 per day for a similar group previously reported,[1,2] and treated with the 3 cc. material.

TABLE 2.—THE AGE, TIME ELAPSED AFTER ONSET OF TREATMENT FOR ERYTHROCYTE COUNTS TO REACH ABOUT 4,500,000 AND 5,000,000 LEVELS AND THE AMOUNTS OF LIVER EXTRACT USED IN THE 28 PATIENTS OF TABLE 1.

Case No.	Age.	Weeks to 4.5+ m.	Weeks to 5.0+ m.	Total No. of injections.	Total amount of liver, gm.*
1	27	5 (4.55)	6 (5.19)	6	600
2	60	6 (4.71)	11 (5.37)	8	800
3	68	6 (4.85)	8 (5.88)	6	600
4	71	6 (4.72)	8 (5.03)	10	1000
5	63	6 (4.63)	8 (5.49)	9	900
6	61	5 (4.69)	9 (5.08)	10	1000
7	57	3 (4.57)	5 (5.55)	7	700
8	68				
9	63	8 (4.83)	13 (5.08)	10	1000
10	69	7 (4.41)	20 (5.80)	15	1500
11	65	6 (4.75)	7 (5.60)	4	400
12	61	8 (4.69)	17 (5.39)	8	800
13	42	7 (4.69)	16 (5.25)	13	1300
14	46	7 (4.82)	11 (5.78)	11	1100
15	55	4 (4.63)	5 (5.60)	6	600
16	70	10 (4.83)	20 (5.19)	12	1200
17	65	5 (4.96)	7 (5.52)	5	500
18	58	4 (4.49)			
19	61	8 (4.55)			
20	47	3 (5.14)	3 (5.14)	5	500
21	41	4 (5.65)	4 (5.65)	7	700
22	54	4 (4.46)	8 (5.16)	5	500
23	52	3 (4.85)	5 (5.61)	8	800
24	45	3 (4.53)	4 (5.11)	7	700
25	77	9 (5.36)	9 (5.36)	6	600
26	64	4 (4.48)	16 (5.18)	10	1000
27	64	3 (4.48)	5 (5.03)	7	700
28	75	3 (4.81)	6 (5.09)	9	900

* The figures in this column indicate the total amount of liver from which the extract was prepared that was administered from the beginning of treatment during relapse to the time that the erythrocyte level reached 5,000,000 or more.

Erythrocyte counts were made at the end of 4 weeks on 24 of the patients. In 17 instances the level had reached 4,000,000 or more and in only 1 instance was the level below 3,500,000 at this interval. In 19 instances a level of 4,500,000 had been reached within 6 weeks of the onset of treatment and within 8 weeks after treatment was begun the erythrocyte level was over 5,000,000 in 15 instances, as shown in Table 2. Failure of the blood to reach 5,000,000 or more within about 8 weeks or less (Table 2) was usually due either to failure on the part of the patient to appear regularly for treatment or for blood counts at the proper intervals. The

amount of material used before reaching this level averaged approximately 1 cc. prepared from 100 gm. of liver each week.

Ten of the patients (Cases 10, 12, 13, 14, 15, 19, 21, 23, 24 and 26) received their initial treatment as ambulatory patients and in most instances continued at their usual occupations. This has apparently made little difference in the rate of improvement in most instances. Three cases, however, warrant special comment.

The patient shown as Case 10 has been under treatment with rather large amounts of whole liver, peroral liver extract or ventriculin since June 10, 1927. During this time and until the intramuscular injections were started she has remained in a fair state of health but with an average erythrocyte count of only 4,000,000. The maximum level reached at any time was 4,800,000. She states that since starting the 1 cc. injections on July 16, 1935, she has felt better than at any time during her illness, and the extreme hyperesthesia of the hands and fingers, which made life miserable for her, has practically disappeared for the first time. The erythrocyte count has averaged above 4,500,000 since 6 weeks after treatment was started and has averaged above 5,000,000 for 2 months, while receiving an injection of 1 cc. at 8-day intervals.

Case 19 began treatment for the first time on January 24, 1935, as an ambulatory patient. She has continued at unusually hard work as a housekeeper throughout her entire period of treatment and without adequate rest. It is a well-known fact that rest favors the production of erythrocytes, whereas fatigue acts to slow-up their production. This patient has required unusually large amounts of material during a period of nearly a year in order to maintain her blood in a fairly satisfactory state (an average of about 4,500,000). Data concerning maintenance treatment is not contained in Table 3 because her treatment was changed to injections of 3 cc. material during that time.

One other patient (Case 13) deserves special comment. During her early treatment as herein recorded she developed an acute attack of appendicitis, was operated upon and in spite of this reached a level of over 5,000,000 in 16 weeks. Except during her period of hospitalization for the operation she continued with her duties as a housewife, caring for several children.

Maintenance Requirements. Perhaps the most critical and important means of evaluating the efficiency of the various substitutes for liver is the determination of the amount of the antianemic material that is necessary in order to maintain the erythrocyte count at a normal level. In order that this procedure may be of distinct value the interval of maintenance observation should as stated, cover a period of time of not less than 6 months, and longer intervals are preferable.

The data obtained in connection with the maintenance treatment of 21 patients by means of intramuscular injections of the 1 cc. extract are shown in Tables 3 and 4.

TABLE 3.—DURATION OF MAINTENANCE TREATMENT, INTERVAL BETWEEN INJECTIONS OF 1 CC. OF LIVER EXTRACT DERIVED FROM 100 GM. OF LIVER AND THE AVERAGE ERYTHROCYTE COUNTS DURING THE ENTIRE PERIOD OF OBSERVATION FOR 16 OF THE CASES OF TABLE 1.

Case No.	Duration of maintenance, weeks.	Average interval between injections, days.	Average R.B.C. count, millions.
4	33	10	5.00
6	37	16	4.97
3	24	17	4.86
5	36	17	4.80
12	25	18	4.87
28	53	19	5.26
2	30	21	5.34
7	39	21	5.64
22	28	22	4.92
24	39	23	5.65
11	52	23	5.83
1	34	24	5.41
17	32	25	5.57
23	44	26	5.26
27	48	26	5.35
25	27	28	5.45

In Table 3 are presented the data obtained in 16 of the 28 patients, first treated during relapse who have been observed for from about ½ to 1 year after the erythrocyte level had reached 4,500,000 or more.

The results shown compare favorably with data previously obtained[4] with treatment by means of intramuscular injections of 3 cc. of liver extract derived from 100 gm. of liver (Lederle) in a series of 89 patients treated for intervals varying from ½ to 2½ years. In this group the average interval between injections of one vial or 3 cc. was approximately 4 weeks, whereas in the group of patients whose data is recorded in Table 3 the average interval between injections of 1 vial or 1 cc. is approximately 3 weeks. A larger series of cases observed over a longer interval of time might easily favorably influence this interval.

TABLE 4.—COMPARISON BETWEEN THE DURATION OF MAINTENANCE TREATMENT, INTERVAL BETWEEN INJECTIONS OF 1 AND 3 CC. OF LIVER EXTRACT DERIVED FROM 100 GM. OF LIVER AND THE AVERAGE ERYTHROCYTE COUNTS DURING THE ENTIRE PERIOD OF OBSERVATION FOR 5 PATIENTS.

Case No.	Initial R.B.C. count, millions.	Duration of maintenance, weeks.	Average interval between injections, days.	Average R.B.C. count, millions.	No. of injections.	Amount each injection, in cc.*
29	4.68	48	17	4.40	20	3
	4.45	57	15	4.65	27	1
30	4.68	59	16	4.97	24	3
	5.19	59	13	4.74	31	1
31	4.82	97	14	4.85	48	3
	4.19	55	19	5.04	20	1
32	5.24	83	28	5.19	21	3
	5.19	57	25	5.19	16	1
33	4.61	105	23	5.23	31	3
	5.05	58	18	5.29	23	1

* Each injection of 1 or 3 cc. represents 1 vial prepared from 100 gm. of liver (Lederle Laboratories, Inc.).

Further evidence of the similarity of the efficiency of these two concentrated and highly potent extracts is shown in Table 4. It is to be remembered that these patients were chosen as test subjects for the 1 cc. extract because they had been found to require somewhat more of the 3 cc. material than the average of the group treated, as described in the preceding paragraph. The interval between injections is essentially the same with the use of either extract and the average interval of 19 days for the entire period on the two extracts is similar to the average interval between injections of 1 cc. as shown in Table 3.

In the 21 cases reported in Tables 3 and 4 erythrocyte counts have been made on essentially each return visit of the patient for injection. An occasional count has been missed through unavoidable circumstances. It has been our aim, as in previously reported data,[3,4,5] to maintain the erythrocyte level at or above 5,000,000 cells per c.mm., for the cells are usually found to remain normal in all demonstrable respects under those circumstances. Only rarely, in this reported group, have we failed to maintain such an average and this failure has usually been dependent upon a temporary drop in the count caused by an intercurrent infection or complication which has not been taken into account in this discussion in the interest of brevity.

Discussion. The advantages, to both the patient with pernicious anemia and his physician, of the use of a highly concentrated liver extract for intramuscular injection in which a high degree of potency has been retained, so that relatively small dosage is needed during relapse in order to produce prompt and striking increases in the number of erythrocytes and which need be administered only infrequently in order to maintain a normal state of the blood over an extract for peroral use necessary in large daily dosage and particularly over the use of extracts of low concentration or potency for parenteral use, are obvious. These advantages have been previously stated so need no further discussion here.[6–11]

The data presented herein demonstrate the high degree of efficiency of this newest and most highly concentrated liver extract which has been developed on a commercial scale for parenteral use. The evidence is in part based upon a comparison with a concentrated extract previously demonstrated to retain a high degree of potency.[3,4] The comparison is made primarily upon the basis of the value of the extract in producing erythrocytes in patients treated during relapse and upon its efficiency in maintaining a normal state of the erythrocytes during intervals of time varying from about 6 to slightly more than 12 months.

Little attention has been paid to the reticulocyte rise as an indication of the effectiveness of this material, for this phenomenon has little value in determining the comparative efficiency of extracts. Observation only of the magnitude of the reticulocyte rise gives

merely an indication of the presence of potency, but not of its degree of potency.[2] The aim of treatment of the patient with pernicious anemia is to produce as quickly as possible a normal erythrocyte count and to maintain a normal state of the blood and the best state of health possible for each patient.[5] The most efficient means of doing this is to use that form of therapy which will accomplish the desired end with the least expense and inconvenience for the patient. Consequently any determination of potency which will be of practical value to the physician in demonstrating what extract is best to use because of its efficiency must be based on its ability to produce erythrocytes and to maintain the blood in a normal state (5,000,000 erythrocytes per c.mm. of blood) in a fairly large group of cases treated with a more or less uniform dosage. This has been done in the treatment of the patients as herein reported.

Although satisfactory erythrocyte increases have been produced during a period of 4 weeks with the use of as little as two vials (2 cc. prepared from 200 gm. of liver) and the average maintenance dose has been as little as one vial (1 cc. prepared from 100 gm. of liver) given at intervals of about 21 days, this has not been true of all patients. Consequently, and because it is best to give maximum rather than minimum amounts for the patient's best interest, one should give injections of more material than that shown as the average unless the erythrocyte level may be checked accurately and at rather frequently intervals so that the dose may be varied as may be indicated by the condition found.

With the use of less concentrated and less potent material it is obvious that injections must be given more frequently and in larger quantity. Although such an extract has obvious disadvantages, for both physician and patient, particularly as to technique of administration and discomfort to the patient, a less obvious but important disadvantage to the patient is that of the expense. One cannot substitute one extract for another, vial for vial or quantitatively, any more than different preparations of digitalis, thyroid substance or vitamins are so interchangeable, for the concentration and potencies vary. Until a system is available whereby the potency may be expressed in units, the safest means of assuring the patient of the best material is on the basis of the amount of potent material, efficient in erythrocyte production, which is present in extract derived from a known quantity of liver.

The material used in this study (1 cc. derived from 100 gm. of liver) has been demonstrated to be essentially equivalent to an extract previously shown to contain a high degree of efficiency; that is, 3 cc. derived from 100 gm. of liver was found to have the erythrocyte-producing or maintenance potency of 30 to 50 or more times that of the amount of liver from which it is prepared, if that liver were given by mouth.[6,7] The high degree of potency of the

3 cc. extract has been confirned, on the basis of the demonstration of its erythrocyte-producing effect during relapse by Connery and Goldwater,[12] and by Alt,[13] and Connery and Goldwater,[14] by determination of the maintenance requirements during periods of 6 months or more. In both studies the average interval between injections of 3 cc. material derived from 100 gm. of liver was 2 to 3 weeks in order to maintain the erythrocyte levels at or near 5,000,000 per c.mm. of blood.

The degree of potency retained in the extract used in the treatment of the patients reported herein is further demonstrated by a comparison of its effect with that of other liver extracts which have been tested for erythrocyte-producing effect and for maintenance requirement. The methods of recording data varies so much in the reports that no attempt will be made to analyze them in detail, but for further information the reader is referred to the original articles. Unfortunately few reports are available concerning the maintenance requirements of other extracts which include a sufficiently long period of observation or number of patients to give a satisfactory indication of the value of the extract. In analyzing data of this sort one must also bear in mind the importance of the erythrocyte levels which are maintained, for it takes an appreciably greater amount of material to maintain the levels at 5,000,000 or higher than it does to maintain them at lower levels.

Zerfas[15] observed the erythrocyte increases during a period of 1 month in 61 patients treated during relapse with the daily ingestion of extract prepared from 300 to 1000 gm. of liver. The erythrocyte count reached 4,000,000 or more during this interval in only 5 patients. Fouts and Zerfas[16] report the maintenance of "normal" erythrocyte levels in 38 patients during an average period of 3 years with extract derived from 300 gm. or less (average, 223 gm.) of liver, whereas the levels in 21 patients were not maintained with an average daily ingestion of extract derived from 381 gm. of liver. Isaacs, Sturgis, Goldhamer and Bethel[17] found that in 8 patients with an average erythrocyte level of 840,000 it required 63.9 days to reach an average count of 4,350,000 with an average gain of 56,000 cells per day during this period, using intravenous injections of extract, probably 20 cc. prepared from 100 gm. of liver, at weekly intervals. The exact dosage is not stated. In 10 patients, similarly treated, with an average initial level of 1,420,000 it required 50 days to reach an average level of 4,290,000. The average daily gain during the entire period was 61,000. In a third group of 21 patients with an average initial count of 2,630,000 it took 42.9 days to reach an average of 4,380,000. They further report an average daily gain of 98,000 for the first 2 weeks of treatment in the first group and of 82,000 in the second group. This is to be compared to average increases of 137,000 and 105,000, respectively, in two groups with comparable initial levels and treated with the 1 cc.

material as recorded in Table 1. Isaacs and his co-workers maintained "normal" erythrocyte levels in 56 patients during a period of from 6 to 17 months with intravenous injections of 20 cc. of extract once each month. Meyer, Richter and Ivy[18] observed average daily gains of 59,000 erythrocytes in 13 patients treated with an average daily subcutaneous or intravenous injection of 1.6 cc. of equine liver extract for periods of from 9 to 73 days. They report that each 1 cc. is "equivalent" to 10 gm. of liver. Meyer, Richter and Legere[19] report the results of treatment of 6 patients with subcutaneous injections of extracts prepared from pre-digested equine liver (with stomach mucosa). Injections representing the extract from 475 to 1825 gm. of liver were given during periods of from 16 to 73 days with an approximately similar daily gain. They conclude that this material has slightly greater potency than was present in their equine liver extract. It is difficult to use their data for the purposes of comparison because of the varied periods of treatment, but the indications are that the material is of relatively low potency as compared to the material herein considered. Bethel[20] has reported the length of time necessary to bring the erythrocytes to a level of 4,000,000 in 150 cases treated with weekly intramuscular or intravenous injections of 10 to 20 cc. (prepared from 50 to 100 gm. of liver). In those patients with initial erythrocyte counts below 2,500,000 it took 5 weeks, whereas it took only 4 weeks in those with initial counts between 2,500,000 and 3,000,000 and lesser periods of time in those with higher initial counts.

Conclusions. The material used in the treatment of the patients under consideration in this study has an antianemic effectiveness for erythrocyte production during relapse of from 20 to 40 times the amount of liver from which it is prepared and for maintenance purposes from 50 to 70 times the amount of liver from which it is prepared if that were ingested. It is also apparent that this extract for intramuscular injection so prepared that 1 cc. is derived from 100 gm. of liver has retained the antianemic potency to an extent entirely comparable to that retained in the most efficient of those less highly concentrated extracts for parenteral use upon which satisfactory potency tests have been carried out.

Therefore, because of its high degree of efficiency, ease of administration and reasonableness of cost, in consideration of its effectiveness, this extract is the ideal one for use.

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EXPERIMENTAL RADIUM POISONING.

I. Bone Marrow and Lymph-node Changes in Rabbits, Produced by Oral Administration of Radium Sulphate.*

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Although the intravenous administration of radium salts in the treatment of sundry ailments has in a few instances resulted in radium poisoning, the great majority of human cases have been

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brought about by ingestion or inhalation of radio-active substances, the victims being chiefly watch-dial painters, chemists, miners and consumers of radium-water nostrums. Nevertheless in none of the experimental studies of this condition have radio-active materials been administered orally. This fact is of interest, for, as will be seen, certain discrepancies exist between the lesions that have been found in experimental animals and those in the humans.

Lacassagne and his coworkers,[1] in 1925, reported the production of acute and chronic forms of nephritis together with marked changes in the blood-forming centers by the intravenous and intraperitoneal injection into rabbits of lethal doses of polonium, a decay product of radium emitting only alpha rays. Within 5 days the bone marrow showed an almost complete loss of erythrocytic and leukocytic elements and presented the histologic picture of an acellular fatty marrow. Sabin and her co-workers,[2] in 1932, studying the effects of the intravenous injection of radium chlorid and mesothorium on the lymph nodes and bone marrow of rabbits, found that the fundamental damage was in the stem cells of the lymphoid tissues. They could find no significant changes in the granulocytic cells of the marrow. They concluded that the erythroid tissues are less susceptible to radio-active material than the lymphoid tissues, although they observed that an early mild anemia of secondary type, developing from peripheral destruction, might eventually be changed to one of primary type through a decreased maturation of primitive cells in the marrow. Two of the 7 rabbits in their series, surviving 11 and 19 months respectively, developed osteogenic sarcomata due apparently to storage of radio-active material in the bone. Thomas and Bruner[3] in 1933 made a study of chronic radium poisoning in rats, produced by subcutaneous injection of radium chlorid. In a series of 8 albino rats, these authors reported the occurrence of marked loss of weight, pathologic fractures, secondary anemia, hyperplasia of the marrow in the central two-thirds of the shafts of the long bones, and aplasia of the marrow of the flat bones. The hyperplastic changes in the marrow consisted of an increase in the myelocytic cells with an abundance of megakaryocytes. They also noted damage to the lymphoid tissues and parenchymatous organs. Foci of extramedullary myelopoiesis were found in the spleen, lymph nodes and liver.

De Laet,[4] in his general review on the deleterious effects in humans from the handling of radio-active substances and exposure to Roentgen rays, cites the occurrence of the following blood dyscrasias; aplastic anemias, leukopenias, leukemias (myelogenous and lymphatic) and occasionally primary anemias. Most of the cases reviewed had not been autopsied nor had studies of the bone marrow been made to determine the exact types of blood dyscrasia. In Martland's[5] observations on victims of radium poisoning by ingestion and inhal-

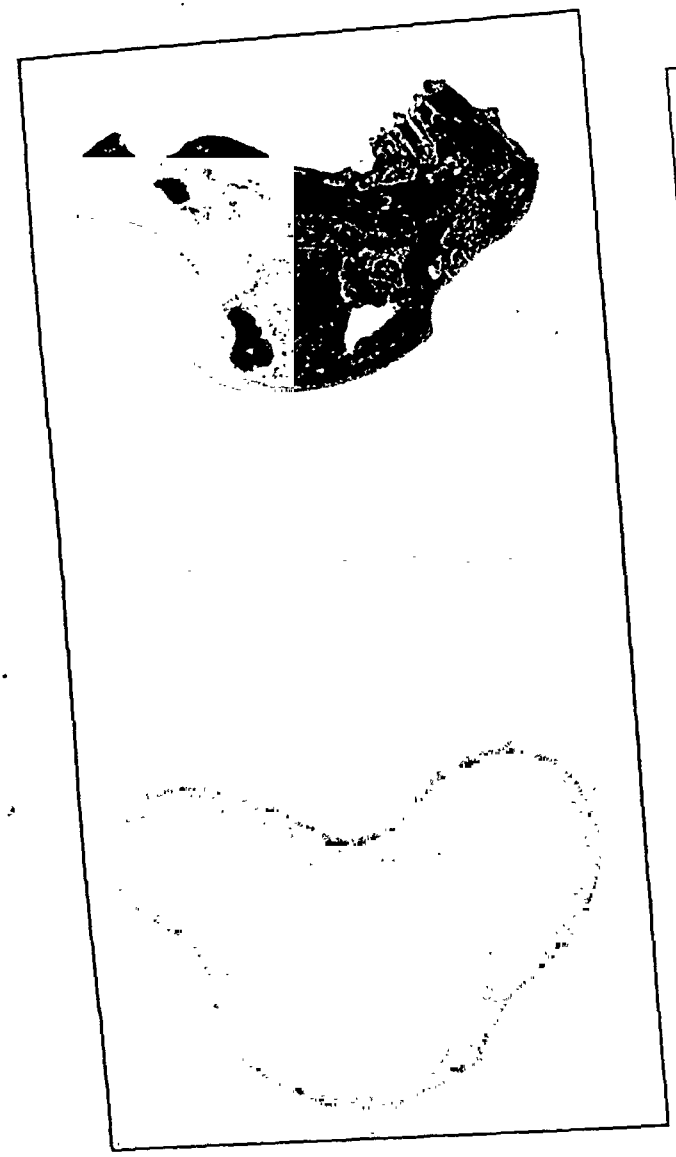


FIG. 1

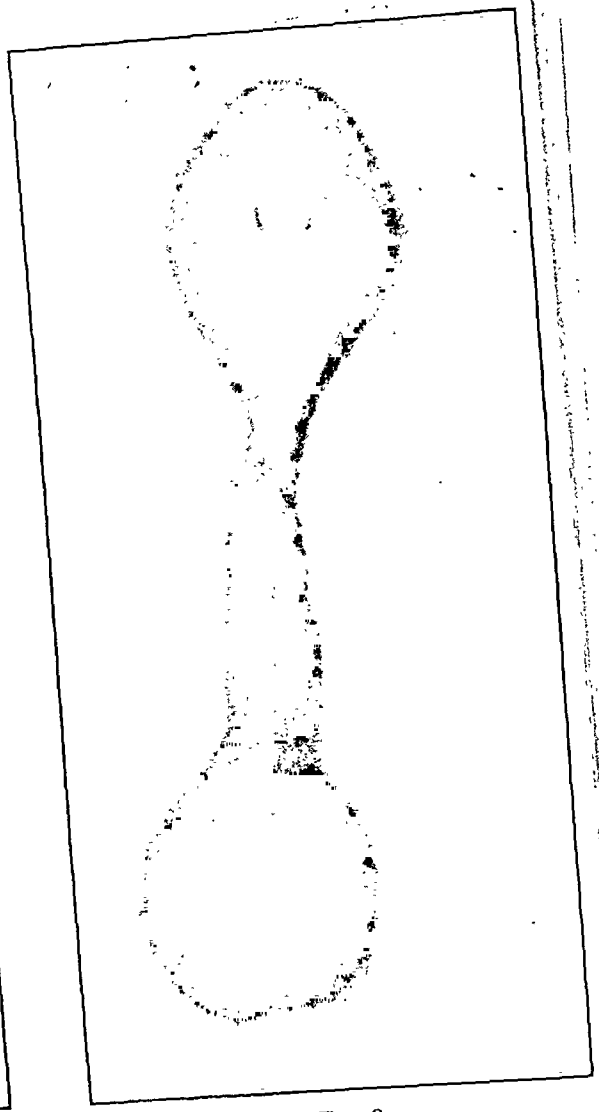


FIG. 3

FIG. 1.—*Above.* Mandible showing osteoporosis and large fenestrations in mandibular plate. Due to fragility of bone the mental process with incisor tooth was separated in preparation. *Below.* Autophotograph of the same mandible indicating presence of radium in bone.

FIG. 3.—Autophotograph of femur of Rabbit 4 showing patchy distribution of radium as the result of bone destruction and reconstruction in a later stage of radium poisoning. This bone was not the seat of a fracture, although the peculiar radium distribution might suggest fracture of the shaft.



FIG. 2.—Autophotograph of various bones of Rabbit 1 showing more or less uniform distribution of radium in an early stage of radium poisoning.

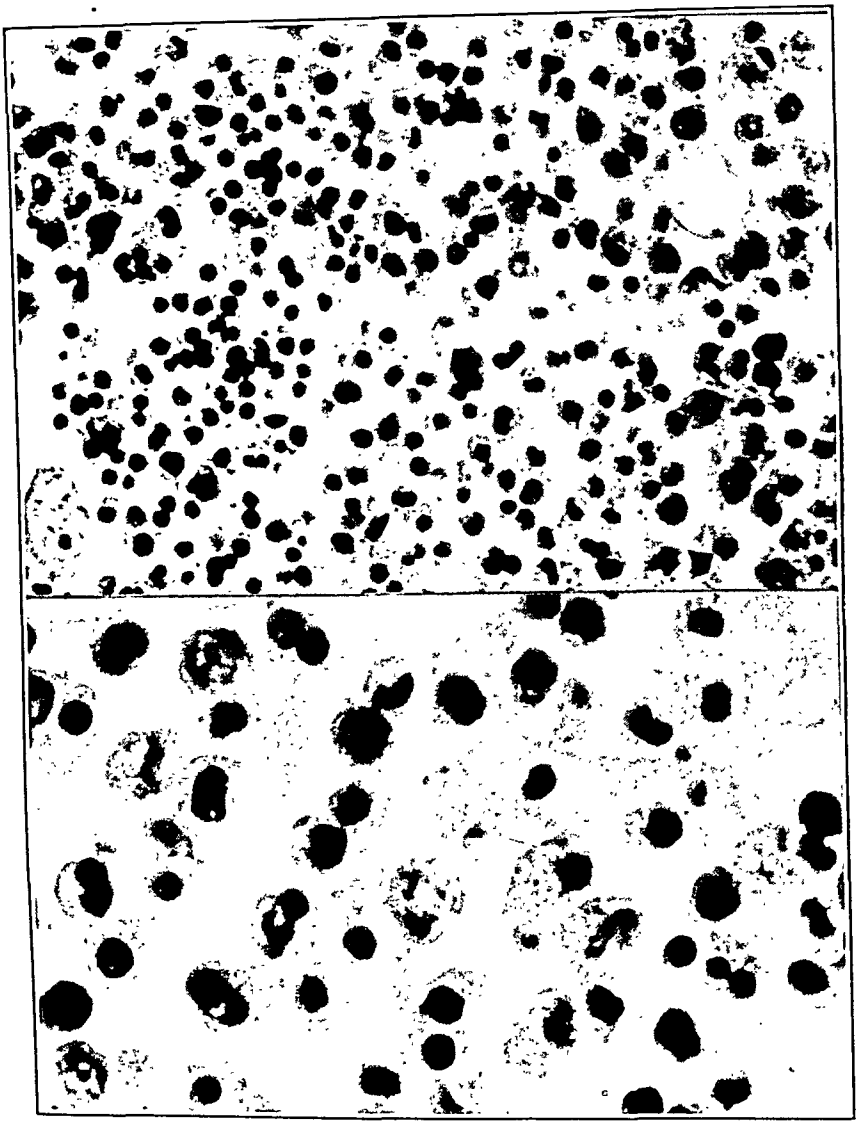


FIG. 4.—*Above.* First stage of hyperplastic marrow, the predominating cells being of the erythroblastic series. *Below.* High power of above shows the majority of the cells to be erythroblasts and normoblasts.

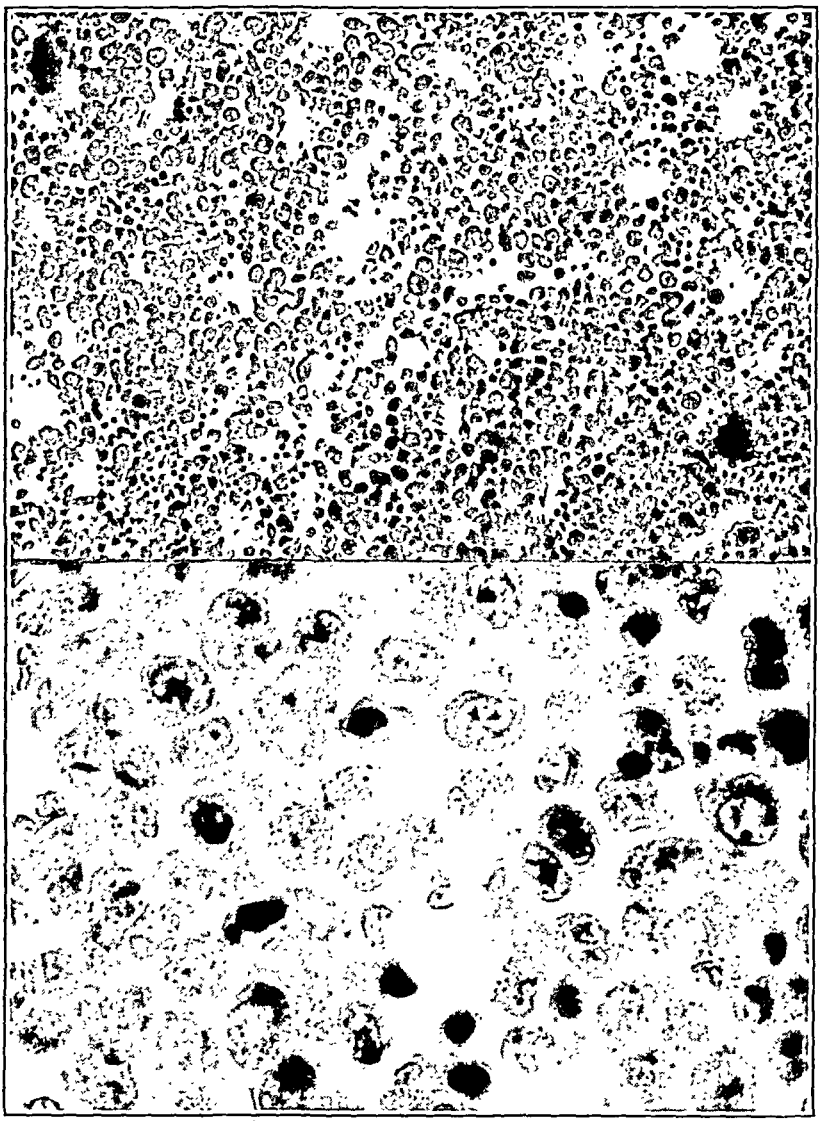


FIG. 5.—*Above.* Marked hyperplasia of marrow at midfemur, the predominant cells being myelocytes among which a few clumps of erythroblasts and normoblasts may be seen. *Below.* High power of above showing the majority of the cells to be myelocytes with a few late erythroblasts and normoblasts.

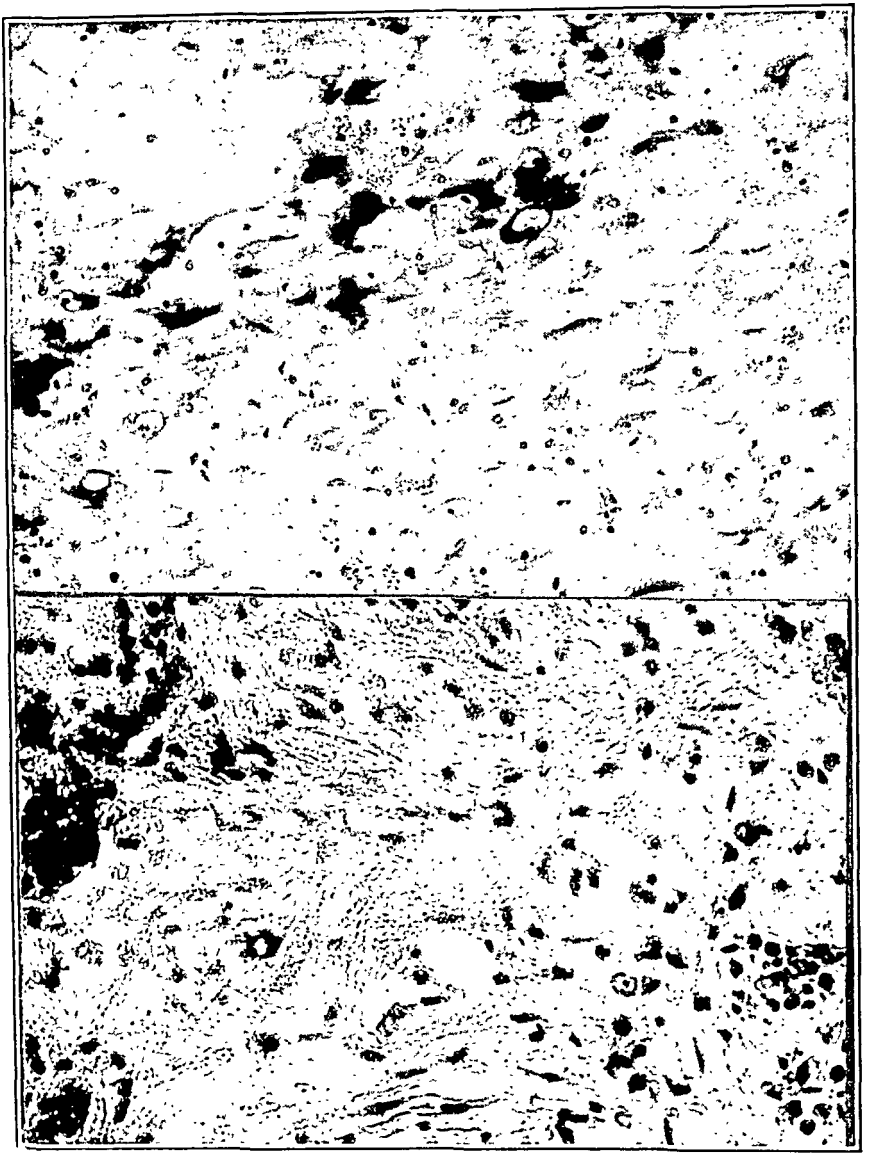


FIG. 6.—*Above.* Mucoid degeneration of marrow: the strands of large dark cells are degenerating reticulum cells. *Below.* Fibroblastic replacement of degenerating marrow.

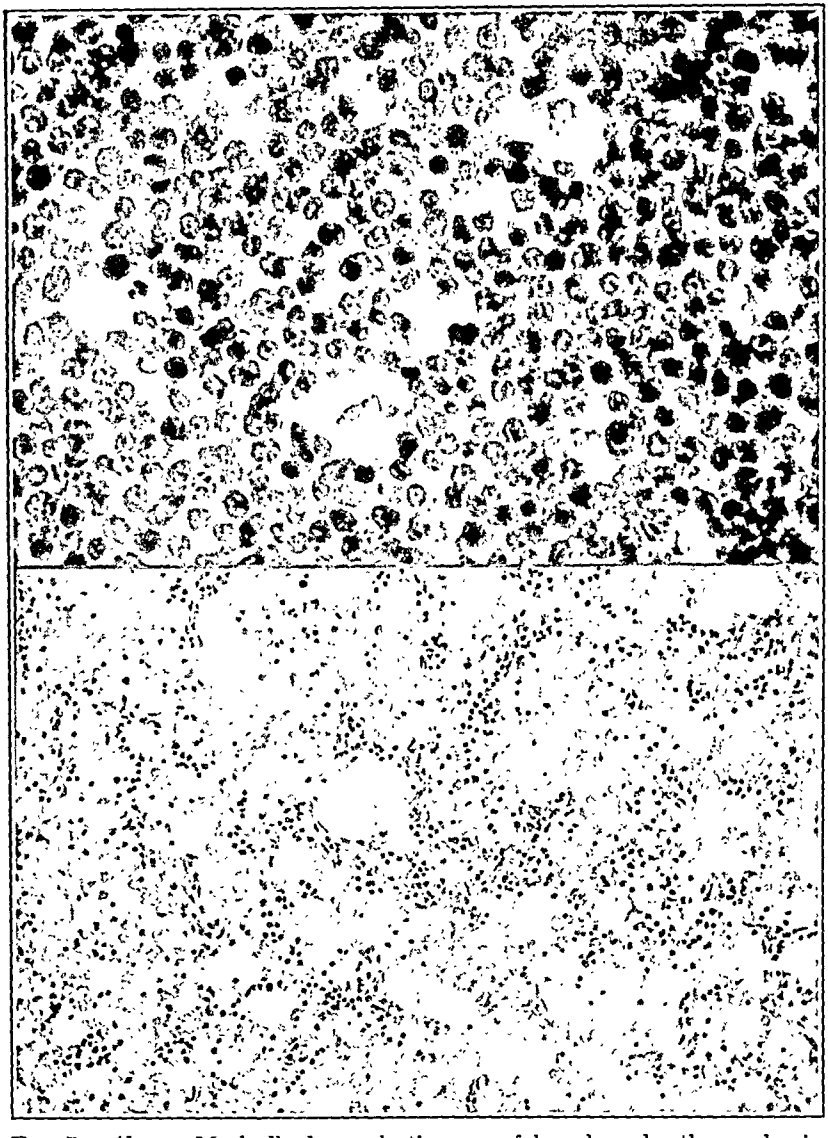


FIG. 7.—*Above.* Markedly hyperplastic area of lymph node, the predominant cells being lymphoblasts among which are a few mature lymphocytes and degenerating stem cells. *Below.* Marked cellular depletion of lymph node: the faint outlines of degenerating stem cells in a background of cell débris can be seen.

ation there were found at autopsy leukopenic anemias of the regenerative type and marked changes in the marrow.

In the light of the disagreement between the various experimental findings and the findings in the human cases there still would seem to be some doubt as to the exact nature of the anemias and the lymph gland and marrow changes. We have thought therefore that study of the bone marrow and other tissues from animals that had been given radium salts *per os* might help to explain the pathogenesis of these blood tissue alterations.

Material and Methods. Four rabbits 6 months of age were used, of which 2 were males, each weighing 2700 gm., and 2 females, each weighing 1800 gm. The animals were kept on a normal and adequate standard diet throughout the experiment. Each animal was fed several drops of a suspension of radium sulphate in glycerin by a medicine dropper 3 times daily for a period of 90 consecutive days. By the end of this period each rabbit had received orally approximately 100 micrograms of radium sulphate. Glycerin was found to be a suitable vehicle and the animals seemed to enjoy the sweet taste, thus assuring ingestion of most of the radium salts. The rabbits were observed daily for physical changes, and blood studies were made bi-weekly. The animals survived for 3, 12, 13 and 18 months, respectively, after the cessation of radium administration.

In studying the marrow of our rabbits we employed the procedure recommended by Krumbhaar and Custer.[9] These authors recommend making differential counts of marrow sections, a procedure which gives accurate information concerning the status of the hemopoietic tissue.

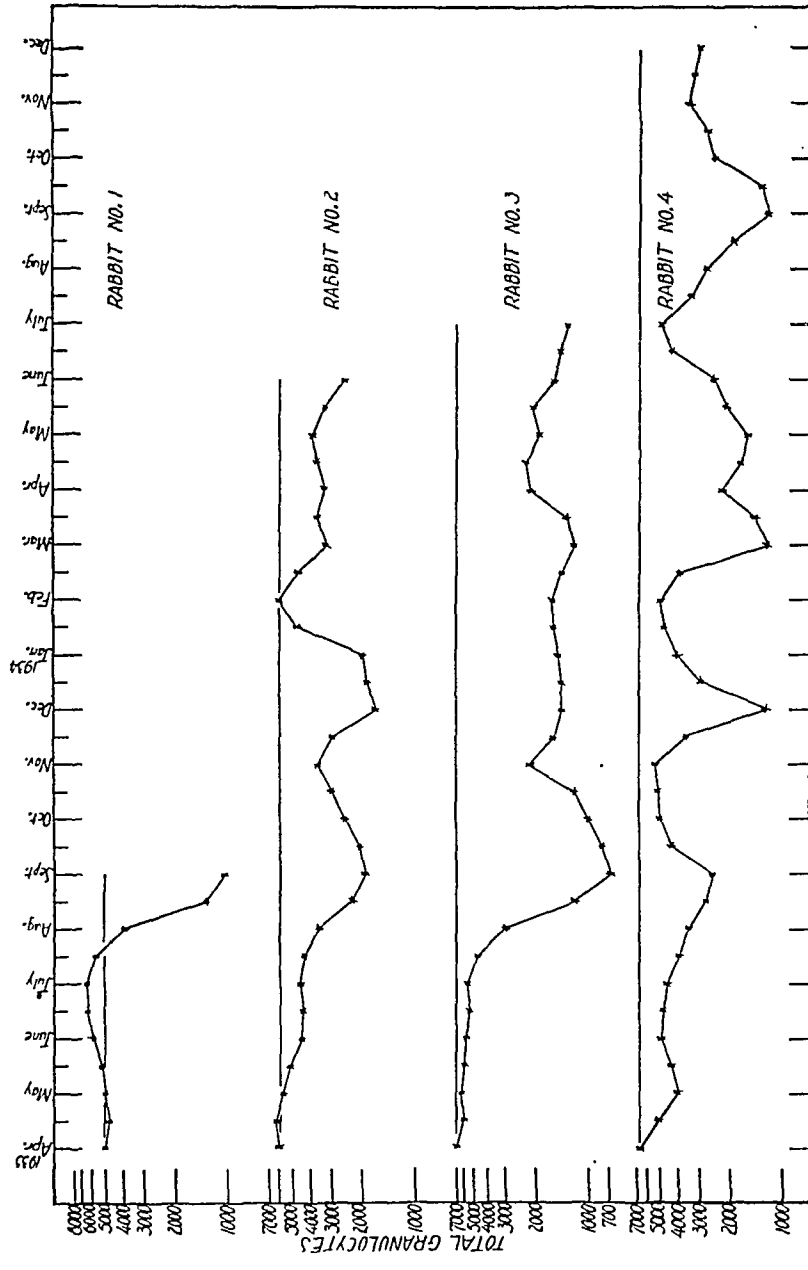
Physical Changes During Life. For the first 2 months of the radium administration the animals showed no abnormal changes. During the third month, however, the lower incisor teeth of all showed a brown mottling. In the next few weeks this mottling became more marked and the teeth were observed to be definitely shortened. Associated with these dental changes was a gingivitis, and in manipulating the jaws during the administration of the radium there was manifested a progressive tenderness.

One month after cessation of radium administration a diffuse thinning of the fur occurred in all the animals and a month later definite local areas of alopecia were observed in the peri-orbital regions and over the hind legs. No further physical changes were noted until 3 months after cessation of radium administration when Rabbit 1 developed a spontaneous fracture of the third lumbar vertebra associated with a flaccid paralysis of the hind legs. Two days later the animal died. The necropsy findings will be discussed later.

During the following 6 months the lower incisor teeth of the remaining rabbits became shortened to about 2 mm. above the gum margins. The upper incisors showed to a lesser degree the same changes, the sharp incisive edges being worn off (abraded) with the formation of broad occluding surfaces. In the meantime these animals developed abscesses of the jaw and Roentgen ray examination revealed irregular areas of rarefaction of the mandibular plates. The abscesses subsided spontaneously. By this time (9 months after cessation of radium administration) Rabbits 2, 3 and 4 had lost 350, 250 and 100 gm. respectively in weight. Five weeks later Rabbit 3 developed spontaneous fractures of both femora and tibiæ and lived 7 weeks longer without developing any further visible complications. In the meantime Rabbit 2 developed multiple fractures of both hind legs and died the following day, 12 months after the end of treatment.

Thirteen months after the end of radium administration the only surviving rabbit (No. 4) developed an abscess of the jaw which perforated

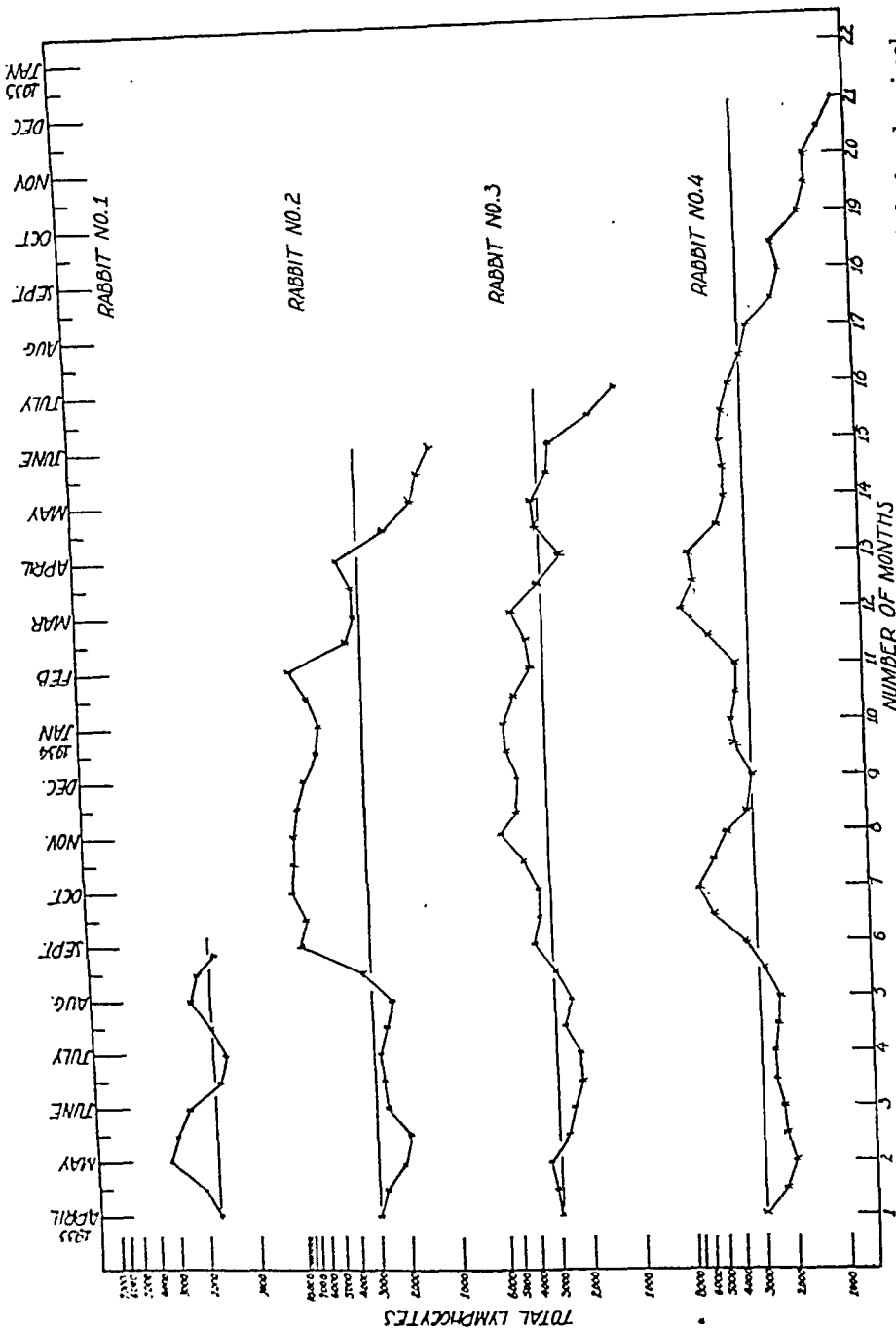
and drained into the buccal cavity. Roentgen ray studies at this time revealed large irregular areas of rarefaction in the right mandibular plate. Aside from the fact that the lower incisors were worn down to the gum margin, this animal showed no physical changes until one day before death



GRAPH 1.—Representation in absolute figures of the lymphocyte counts, throughout the survival period of each animal.

when it developed a spontaneous fracture of the lower lumbar vertebra with an associated flaccid paralysis of both hind legs. The following day (18 months after radium administration) the rabbit was killed by intravenous injection of air.

Changes in the Circulating Blood. With the exception of one animal (Rabbit 1) that lived only 3 months after treatment, all showed mild pro-



GRAPH 2.—Representation in absolute figures of the granulocyte counts throughout the survival period of each animal.

gressive anemia with slight remissions. There was a gradual decrease in hemoglobin in all of the animals and the color index, despite slight fluctuations, showed a progressive fall. The blood smears showed signs of erythro-

cytic activity by an increase in the number of reticulocytes and the appearance of nucleated red cells. There was a moderate degree of poikilocytosis and anisocytosis. In a similar manner, despite occasional remissions, all of the animals (except Rabbit 1) showed a progressive fall in the total number of leukocytes. However, the differential counts revealed a prolonged period in which there were relative and absolute increases in lymphocytes, though these were not always concomitant (Graphs 1 and 2). These periods bore no relationship to the total number of leukocytes. In one animal (Rabbit 2) there was a marked terminal leukopenia.

Six months after radium administration various evidences of degeneration were seen in the granulocytes and lymphocytes. In the former the cell membrane very rarely remained intact in the blood smears, the cytoplasmic granules being intercellularly dispersed. The nuclei stained poorly and the nuclear membrane was indistinct. Occasionally the nuclei were found to be extruded. The lymphocytes stained poorly and showed fragmentation of the nuclei.

Necropsy Findings. Rabbits 1 and 4 that developed spontaneous fractures of the lower lumbar vertebræ with cord compression showed retroperitoneal hemorrhages which had infiltrated the psoas muscles. In Rabbits 2 and 3 there were hemorrhages into the soft tissues overlying the fractures of the long bones.

The lymph nodes and spleens of Rabbits 2, 3 and 4 were generally decreased in size. No other gross changes were observed in the thoracic, abdominal and pelvic organs.

In all of the rabbits the long bones, especially the femora and tibiæ, showed, in addition to the fractures described above, a thinning and porous condition of the compact bone. There was also marked thinning of the cortex of the flat bones and in some of these the red marrow could be easily seen through the thin cortex. The most striking pathologic changes, however, were found in the mandibles where the mandibular plates were extremely thinned and in several instances fenestrated (Fig. 1). All of the bones were very fragile. Though no macroscopic tumors of the bones were noted, in Rabbit 3 there were numerous nodular bony enlargements measuring 4 to 6 mm. in size in many of the ribs. None of these nodules occurred at the costochondral junctions.

The marrow of the long bones, ribs and vertebræ was of the red variety in all of the animals except Rabbit 4 where it was pinkish-gray in color. Near the epiphyseal ends of the femora of this animal a few grayish-white areas 2 to 3 mm. in size were seen.

Microscopic Findings. The most important histologic changes were found in the bones, teeth and hemopoietic organs.

The osseous system, especially the femora, tibiæ, ribs, vertebræ and mandibles, showed a marked generalized osteoporosis and most of the compact bone was necrotic. There was atrophy of the trabeculæ in the epiphyseal ends of the long bones and widespread subendosteal and subperiosteal cortical resorption. Numerous Howship's lacunæ were seen with only occasional osteoclasts. The Haversian canals were enlarged and their walls were also irregularly indented by Howship's lacunæ. There were extensive foci of new bone deposition beneath periosteum and endosteum which bore no definite relationship to the sites of the fractures. Much of this new bone was also necrotic. The articular cartilages were extremely irregular in thickness due to marked focal hyperplasia interrupted by areas of necrosis. The nodules on the ribs of Rabbit 3, mentioned above, presented the appearance of bony calluses of healing fractures. The granulation tissue of the callus was exceedingly rich in blood capillaries and numerous giant cells with multiple nuclei were encountered in certain areas. The fibroblastic cells of this granulation tissue were particularly

large, showed immaturity approaching a definite anaplasia and presented many mitotic figures.

Bone Marrow. The general architecture of the marrow in all 4 rabbits was greatly altered. From the marrow of the middle third of the femur a differential cell count was made on each animal and compared with those of normal animals (Table 1).

On analysis of these counts it is found that Rabbit 1 showed a slight hyperactivity of the erythrocytic elements, the reaction being of normoblastic type with slight increase in erythroblasts. The eosinophilic myelocytes were within normal limits. The usual degenerative-regenerative balance of megakaryocytes was noted. In Rabbit 2, where erythropoietic islands were seen to be larger and more numerous than in the former animal, the increased erythropoiesis was of the normoblastic type though showing slight erythroblastic activity (Fig. 4). A moderate proliferative activity of myeloblasts was noted. There was a definite increase in eosinophilic myelocytes. The megakaryocytes were decreased slightly and showed a slight increase in the various degenerative forms.

TABLE 1.—DIFFERENTIAL COUNTS ON BONE MARROW, EXPRESSED IN PERCENTAGE. (EACH COUNT BASED ON 1000 CELLS).

	Control.	No. 1.	No. 2.	No. 3.	No. 4.
Granulocyte Series:					
Myeloblasts	0.4	0.6	2.4	3.0	6.6
Promyelocytes	1.3	0.8	1.6	0.2	1.6
Myelocytes:					
Neutrophils	63.4	55.6	34.9	69.2	54.8
Eosinophils	1.4	1.6	3.3	4.0	8.4
Basophils	0.0	0.0	0.0	0.0	0.0
Metamyelocytes	1.3	0.2	0.3	7.6	11.0
Segmenters (all types)	2.2	0.6	0.4	2.2	0.8
	70.00	59.4	42.9	86.2	83.2
Erythrocyte Series:					
Erythroblasts	3.7	6.8	6.0	8.1	11.0
Normoblasts	24.1	30.2	49.1	5.0	5.0
	27.8	37.00	55.1	13.1	16.0
Thrombocyte Series:					
Megakaryocytes	0.5	0.4	0.3	0.2	0.2
Megakaryoblasts	0.0	0.0	0.0	0.0	0.0
	0.5	0.4	0.3	0.2	0.2
Reticulo-endothelial Series:					
Reticular cells	1.0	2.0	1.2	0.2	0.2
Endothelial cells	0.2	0.4	0.3	0.2	0.2
	1.2	2.4	1.5	0.4	0.4
Lymphocytic Series:					
Lymphocytes	0.5	0.8	0.2	0.1	0.2
Plasmacytes	0.0	0.0	0.0	0.0	0.0
	0.5	0.8	0.2	0.1	0.2

The marrow changes of Rabbits 3 and 4 were more striking than those just described. In both of these animals there was a marked activity in the cells of the granulocytic series with a moderate increase in myeloblasts. However, the predominating cells were myelocytes and many of these

showed mitotic figures. A few scattered mature granulocytes were also found. The increase in myelocytes at the expense of the other marrow elements is suggestive of a so-called "replacement anemia" (Fig. 5). It is also interesting to note that although there was a marked decrease in erythropoietic cells, there was a relative increase in erythroblasts apparently the result of decreased maturation of these primitive cells. The eosinophilic myelocytes were increased, being most marked in Rabbit 4. These at times appeared in small groups or islands. The megakaryocytes were slightly decreased in number but showed an increase in the degenerative forms.

These cellular changes produced striking alterations in the topography of the bone-marrow sections. The proliferating myelocytes occurred in elongated islands many of which coalesced to form broad sheets. Occasional small clusters of erythroblastic cells were scattered throughout the myelocytic masses. Although most of the myelocytes appeared normal there were many which showed degeneration and various stages of cytolysis. There were also found large almost completely acellular areas which presented a mucoid appearance and contained the faint remnants of disintegrating granulocytic cells and occasional reticulum cells. The latter were frequently swollen with vacuolated nuclei and frayed or ill-defined cell margins. These relatively acellular areas showed beginning fibroblastic invasion while in still other regions this replacement had given rise to large fibroblastic and fibrotic patches (Fig. 6). These appearances were interpreted as successive stages of radiation osteitis. Occasionally the hyperplastic myelocytic marrow which represents the early stage of radiation osteitis and the fibroblastic and fibrous marrow, representing later stages, could be seen in a single low-power field. The more advanced changes, however, were more frequently seen near the epiphyseal ends.

Lymph Nodes. The changes in the lymph nodes were more or less uniform throughout all the animals except for slight quantitative variations. In general all nodes showed a marked depletion of lymphoid tissue, the background of the depleted areas presenting a pale pink staining fairly homogeneous appearance in which the faint outlines of nuclear membranes were discernible. In contrast to this depletion, in some nodes of all animals but especially in those of the rabbit that lived only 3 months, there were islands of proliferating stem cells, many showing active cell division. In a few nodes of this animal, as in many nodes of the other animals, the foci of proliferating stem cells showed degenerative and necrotic changes so that in some places only the indistinct nuclear and cellular outlines remained. Along with this change was observed a marked increase in lymphoblasts of the large, medium and small varieties which in some instances replaced the mature lymphocytes of the lymph nodes (Fig. 6). Even in markedly depleted nodes some hyperplastic follicles still persisted. The slight damage to the mature lymphocytes and lymphoblasts as compared to the marked damage to the stem cells was a striking feature of the lesion. In Rabbits 2, 3 and 4, a varying number of megakaryocytes, normoblasts and myelocytes were found in the lymph nodes. In some instances the sinuses were crowded with these myeloid cells but occasionally small islands of these cells were found in the lymph cords.

In summary, the lymph node changes consisted essentially of an initial hyperplasia and subsequent degeneration of the stem cells resulting in hypoplasia of lymphoid elements along with myeloid metaplasia.

Spleen. In general the spleens showed changes similar to those found in the lymph nodes. There was a marked decrease in mature lymphocytes and of the lymphoid follicles and the normal architecture was replaced by numerous primitive cells undergoing degenerative changes similar to those described in the lymph nodes. As a result of this marked depletion the sinuses were found to be widened and empty and presented the appearance

of a spleen from which the cells had been washed. This was especially noted in Rabbit 4. As in the lymph glands islands of myeloid metaplasia were found in the spleens of Rabbits 2, 3 and 4.

The microscopic changes in the teeth and parenchymatous organs will be presented in a future publication.

Summary and Discussion. It has been shown by Seil, Viol and Gordon[6] that 60 to 98% of the radium taken into the human system is eliminated, principally in the feces (90%) and urine (10%). When taken by mouth 65 to 75% is eliminated in the first 4 days and by the 10th day the daily rate of elimination is less than 1%. Thereafter there is a gradual diminution in its removal so that after several years the rate of elimination is down to .002 to .005% per day. In albino rats, Thomas and Bruner,[3] found that 50 to 65% of the radium injected subcutaneously was eliminated within one week of the time of injection. The average retention at the end of 6 to 8 months was 24.6% and 99% of this retained radium was found in the bone ash. We, therefore, feel that it is reasonably safe to assume that in our animals that survived 1 year or longer 10 to 20% of the radium ingested remained in the body tissues and that most of it was fixed in the bone. The animals during life were found to be radio-active by testing with the alpha-ray emanation electroscope.* After death the bones were tested for radio-activity by autophotography[1] that is, by placing the bones on a photographic or Roentgen ray plate for several days. The autophotographs of the radio-active bones of human cases have shown a more or less uniform distribution of radium throughout the skeletal system, although in individual bones the distribution is patchy (Martland[5]). In our Rabbits 2, 3 and 4 a similar patchy distribution in individual bones was noted. The autophotographic areas that showed a decreased radium content were those in which histologic sections revealed the most marked osteoporosis and new bone formation. These observations suggest that the distribution of radium is more uniform throughout all of the bones in the early part of the disease (Fig. 2) while in the later stages as the result of bone absorption and reconstruction the radium content is focally diminished (Fig. 3).

The tissue changes produced in our rabbits by the administration *per os* of radium sulphate may be summarized as follows: gingivitis, alopecia, abrasion of teeth, necrosis of bone, spontaneous fractures, regenerative anemia and hyperplasia and fibrosis of bone marrow. Similar changes and in addition osteogenic sarcoma have been reported in human cases. It is also of interest to note that in our experimental animals as in the human cases the first changes were observed in the jaw and mouth, a condition for which no satisfactory explanation has as yet been advanced. Martland[7] stresses the importance of mesothorium in the production of the extensive

* We are indebted to Dr. Alexander O. Gettler for the electroscopic determinations.

jaw necroses and also the severe anemias in the early acute cases among the radium-dial painters. Our experiments show that changes of a similar nature can be produced by sufficient quantities of radium alone.

Of particular interest are the changes in the blood forming tissues in our experiments since the administration of the radium by mouth was followed by lesions which resemble closely the changes that have been observed in human cases. Our observations would seem to indicate that in the bone marrow radium poisoning produces at first a stimulation of the cells of the erythroblastic series with a preponderance of normoblasts, an effect which is to some extent reflected in the blood picture of this period. Continued action of the radium inhibits maturation of the erythroblasts as evidenced by a slight increase in the number of erythroblasts (Rabbits 3 and 4) despite a decided decrease in the total bone marrow erythrocytic elements. At this stage there is an extensive replacement of erythroid elements by cells of the granulocytic series with the production of the picture of the so-called "replacement anemia."

It is noteworthy that, in the more advanced cases of our series, granulocytic hyperplasia with a preponderance of myelocytes was the outstanding feature of the bone-marrow picture (Table 1), a finding at variance with the observations of Sabin and her collaborators[2] who state that the fact that the bone marrow as a hemopoietic organ is less sensitive than the lymph nodes is shown not only by the lack of change in the granulocytes but also by the slight changes in the red cells.

We were fortunate in being permitted to compare our histologic sections with those of Martland's[7] human series. Aside from the fact that our animals did not develop definite sarcomatous lesions the histologic changes found in the bones and bone marrow of the rabbits showed a striking similarity to those seen in the human cases. This author observed a myeloid hyperplasia which he likens to a "panmyelosis, mimicking multiple myeloma." He found that the majority of the cells of the altered marrow were premature stem cells—"hemocytoblasts, proerythroblasts, and promyelocytes." He saw practically no neutrophilic myelocytes or their mature derivatives, whereas neutrophilic myelocytes constituted the majority of the cells in the hyperplastic marrow of our Rabbits 3 and 4. He found that the only cells of the granulocytic series which approached or proceeded to maturation were the eosinophilic myelocytes which were present in large numbers in the bone marrow but did not appear in the circulating blood. We noted a moderate increase of these cells in the bone marrow especially of Rabbit 4 but also found an increase in eosinophils of the blood.

In contrast to these proliferative lesions in the marrow we also found areas of cellular fibroblastic tissue and acellular fibrous tissue replacing the hyperplastic marrow in Rabbits 2, 3 and 4. These

changes correspond in general to those described by Martland[7] as stages of radiation osteitis, namely, a first or "hyperplastic marrow" stage, a second stage of "cellular replacement fibrosis" and a third or healed stage of "replacement by non-cellular fibroblastic tissue." We did not see any sarcomatous areas arising as he suggested from the cellular fibroblastic tissue, but did observe suspicious areas of hyperplastic fibrous tissue in the periosteal region of the atypical healing calluses. However, because similar areas are frequently found in the vicinity of healing simple fractures and since no metastases could be demonstrated we do not feel justified in designating the condition as osteogenic sarcoma.

The earliest change observed in the lymph nodes was a marked and uniform hyperplasia of the stem cells. Even during this hyperplastic stage degenerative changes were seen in these cells, some showing nuclear damage, while others were found in various stages of cytolysis. In the 3 animals that lived for 12, 13 and 18 months after radium administration, aside from the changes just described there was a decided increase in lymphoblasts in some nodes. The lymphoblasts and mature lymphocytes showed only slight degenerative changes as compared with the marked damage noted in the stem cells. In still other lymph nodes there was found a diffuse depletion of the lymphoblasts and mature lymphocytes and, in some instances, an almost complete atrophy. The earlier lesions in the lymphoid tissue were evidenced by a rise in the number of circulating lymphocytes that began approximately 3 months after cessation of radium administration. This rise was sustained except for slight remissions for approximately 6 months and was followed by a steady fall of lymphocytes with an absolute lymphopenia in the later stages (Graph 1).

The effects of radium on the lymphoid tissue in our experiments may well be divided into the three stages designated by Sabin and her co-workers[2] as "first, a period of stimulation to the stem cells; second, a shift to the immature stage known as the lymphoblast; and third, a depletion of the nodes due to such a damage to the stem cell that the losses in lymphocytes can no longer be made up."

Associated with marked myelocytic hyperplasia of marrow in our more advanced cases should be mentioned the development of myeloid metaplasia in the lymph nodes and spleen, a combination of lesions that perhaps bears a significant relationship to the occurrence of myelogenous leukemia in humans unduly exposed to Roentgen rays or radio-active substances. Rolleston,[8] on the other hand, in his critical review of the literature concerning the harmful effects of irradiation expresses the opinion that the development of leukemia among Roentgen ray and radium workers is probably purely coincidental.

Conclusions. 1. The general features of radium poisoning as observed in human cases have been reproduced in rabbits by oral administration of radium sulphate.

2. Jaw necrosis, a characteristic of the early acute cases among radium dial painters, can be produced experimentally by radium alone without mesothorium.

3. In the bone marrow striking changes are produced, consisting of an early hyperplasia of the erythropoietic elements followed by a decreased maturation of the erythroblasts and the replacement of these elements by myelocytes. Finally this hyperplastic marrow is replaced by fibrous tissue.

4. In the lymph nodes there is noted an initial stimulation of the stem cells with subsequent damage to these cells resulting in depletion and atrophy of the lymphoid tissue. In the circulating blood an absolute lymphopenia is found.

5. The development of myeloid tissue in lymph nodes and spleen associated with the extreme myelocytic hyperplasia in the marrow of our animals suggests that the occurrence of leukemia in Roentgen ray and radium workers may not be a pure coincidence.

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TETRALOGY OF FALLOT (EISEMENGER TYPE) WITH HYPOPLASIA OF THE DEXTROPOSED AORTA.

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An exact forecast of the cardiac lesions that may be found in congenital cyanosis was long considered practically impossible, and the idea, that in morbus ceruleus interauricular septal defect must

always be present, died hard. The profession is greatly indebted to Fallot[1] who, in 1888, published a series of articles on the subject In the course of some years he had seen 3 patients come to autopsy, and was struck by the similarity of the lesions. Following this he collected in all 55 cases, in whom 41 (74%) showed that congenital heart disease associated with cyanosis, especially in adults, is the result of a small number of perfectly definite cardiac malformations. This group of pathologic-anatomic aberrations is represented by the following tetralogy: pulmonary stenosis, interventricular septal defect, deviation of the origin of the aorta to the right, hypertrophy of the right ventricle, almost always concentric in type. Patency of the foramen ovale is entirely an accessory defect. He believed that these 4 anomalies arose in consequence of the stenosis of the pulmonary artery. Others now think that the dextroposition of the aorta may be quite as important an element in their origin. This is borne out by the case reported by Baumgartner and Abbott[2] and the one we report. In these cases there was no real pulmonary stenosis but there was dextroposition of the aorta. In only 1 case of Fallot's series was early cyanosis in this tetralogy wanting,[3] and that might be explained by the fact that the obstruction was in the conus rather than in the pulmonary artery, whose opened and unopened valves were intact. Since this obstruction had an opening the size of a little finger, it may have sufficed for the need of the patient.

It is gratifying to have Dr. Paul White[4] include a translation of Fallot's conclusions in his textbook. It is a recognition of Fallot's distinct contribution to the diagnosis of congenital cyanosis, especially those reaching adult life.

In 1897 Eisemenger[5] reported a case which is sometimes referred to as the tetralogy of Eisemenger, which might better be called the tetralogy of Fallot, Eisemenger complex, as suggested by Dr. Maude Abbott. In this patient, a man of 32, with cyanosis since birth, the findings were interventricular septal defect, dextroposition of the aorta, which was placed astride the septa defect so as to receive blood from both ventricles, right ventricular hypertrophy, a moderately widened pulmonary conus arising normally from the right ventricle, and a somewhat dilated pulmonary artery showing some endoarteritic thickening, but whose valves were smooth and competent. He gives no measurements, but since he says the conus is moderately widened and the pulmonary artery is somewhat dilated, it is inferred that the dimensions were not striking. The aorta was of its usual dimensions, thin walled and smooth. There was no pulmonary stenosis in this case.

Baumgartner and Abbott[2] reported a case of the Eisemenger type in a man of 20 who was found to have an interventricular septal defect, dextroposition of the aorta, with a pulmonary conus, orifice and artery normally developed, but having undergone "dilatation

as a result of influx of blood from the left ventricle through the defect into the pulmonary circulation." They stress the fact that there was no pulmonary obstruction in this case.

The case we present was that of a woman, aged 31, with cyanosis since birth whose heart showed interventricular septal defect, a slightly widened conus arteriosus and a fusiform dilatation of the pulmonary artery; a hypoplasia of the dextroposed aorta, which was so placed as to receive blood from both ventricles; great hypertrophy and dilatation of the right ventricle. The hypoplasia involved both the thoracic and abdominal aorta. The foramen ovale was intact in this case, as it was in Eisemenger's. Here again is a case of tetralogy of Fallot, Eisemenger type, in which there was marked pulmonary dilatation and insufficiency and little, if any, obstruction.

Case Report. The patient, aged 31, of German-American parentage, was 61 inches tall and her weight over a 9-year period ran from 96 to 108 pounds. She was well developed both physically and mentally. Her mother stated that she was born at 8 months and was a blue baby. Her mother never had any rheumatic fever or any other infection, at least during the pregnancy. There is 1 brother who is 37 and in good health.

Her early infections were measles and chickenpox. She had double mumps in 1926 and pertussis the same year. Her tonsils from 1929 on were evidently somewhat infected. Her thyroid was palpable but had no influence on the condition. Her teeth were always good. She had bronchopneumonia twice, and was given to attacks of bronchitis. Always throughout life she suffered from dyspnea on exertion. Up until 9 years she was considered a delicate child, after that she was active, taking part in sports and dancing until she was 15. Her periods began at 12; they were usually profuse, sometimes irregular, and at 15 she had a marked menorrhagia and was admitted to a hospital with the diagnosis of mitral stenosis and a blood count of hemoglobin, 50%; red blood cells, 3,420,000; white blood cells, 6000. After curettement she recovered and was not troubled overmuch by her heart condition until after the birth of her first child in 1924. This child is a perfect specimen of boyhood. After his birth she noticed she had less cardiac reserve, which was still further lowered in September, 1926, when she gave birth to twins at 7 months, who survived but 6 hours. Although she had always shown cyanosis from birth it was worse after these pregnancies. It involved her visible mucous membrane, lips, cheeks, ear tips, fingers and toes and the latter both showed clubbing. Epistaxis was a frequent occurrence and sometimes it was severe as in 1927 and 1930. She was blind for 2 hours after labor in 1926. She had much vertigo and many fainting fits and was once carried unconscious into a hospital from the street. She was always more or less hoarse and it was especially marked after 1926. The postmortem findings confirmed Fetterolf and Norris,[6] who maintained that the recurrent laryngeal paralysis was due to pressure of the enlarged pulmonary artery rather than the enlarged left auricle. The highest early blood count was in 1926 when the hemoglobin was 120%; red blood cells, 5,750,000; white blood cells, 7500. Three counts made in 1928–1929 all showed hemoglobin of from 105 to 110% and red cells over 5,000,000. From that time on until her last illness the counts were nearer normal. The average of many counts was hemoglobin, 88%; red blood cells, 4,350,000; white blood cells, 7830. November, 1934, she developed an acute respiratory infection with a severe cough. This led to marked

failure by congestion and with the consequent passive engorgement the counts rose again. Because of the severity of her condition, through the courtesy of Dr. E. W. Pflueger, who was attending her, she was admitted to the Presbyterian Hospital 18 days before her death. On admission the count was hemoglobin, 140%; red blood cells, 6,250,000; white blood cells, 7800. The average of 4 counts after that was hemoglobin, 120%; red blood cells, 5,620,000, although 200 to 300 cc. of blood were withdrawn before each intravenous injection of an equal amount of glucose solution.

Physical Examination. This is largely a composite picture of the important and more or less constant findings over a 9-year period.

There was usually an epigastric impulse and an exaggerated movement to the left of the sternum about the 3d and 4th ribs. The midsternal thrill was systolic and sometimes diastolic. At the 3d left intercostal space there was sometimes a diastolic thrill. Percussion showed a wide lateral diameter of the heart and increased dullness in the region of the left auricle and pulmonary artery. The first sound at the apex was always short, sharp, exaggerated and snapping; occasionally it was doubled. The second pulmonary sound was usually recorded plus, the aortic second sound was often marked plus and sometimes simply present. The second sound at the apex was usually present. A low pitched diastolic murmur was constantly heard at the pulmonary cartilage and at the apex. This diastolic murmur could be traced from the pulmonary cartilage along the left edge of the sternum to the apex. Sometimes there appeared to be a gap in tracing this murmur, so that it suggested that there possibly was a second diastolic murmur at the apex. Sometimes we thought there was a presystolic exaggeration. There was a systolic murmur at the apex higher pitched, heard also over the midsternum but not transmitted, at least regularly, to the base of the heart. Occasionally a slight transmission to the axilla and the left back is recorded. Only once was there a systolic murmur at the pulmonary area found. It is interesting that the abnormal valves found at postmortem should not have produced a more constant systolic element; the diastolic murmur was never lacking.

The fluoroscopic examination, in 1929, showed an enlarged shadow lying in the region of the great vessels beginning at the level of the 2d rib and extending downward to the 4th rib anteriorly where it joined with the left ventricular shadow. This mass pulsated and the aorta appeared to be posterior to it. The right side of the heart was greatly enlarged. The great vessels measured 9 cm., the heart's transverse diameter was 14.5 cm. and the chest 27 cm.

Again in 1931 the pulmonary artery and right ventricular conus were unusually prominent and pulsated freely.

The films showed as early as 1927 a marked bulging in the upper left segment of the heart silhouette, a rounded enlargement of the right ventricular border and a markedly increased transverse diameter of the heart giving the ventricles a globular shape. This hypertrophied right ventricle pushed the conus pulmonalis upward and this with a widened pulmonary artery gave the prominent pulmonary arc in the curves.

The silhouette (Fig. 1) is much like that of Vaquez and Bordet[7] of their young woman of 25 who had pulmonary stenosis and interventricular septal defect but no cyanosis.

The silhouette of Baumgartner and Abbot's case also shows an exaggerated pulmonary segment in the film, and a globular shadow of the ventricles with increased transverse diameter.

There were many electrocardiograms, they were all essentially like the cuts (Fig. 2). The deflections were rather large, there was never the picture of preponderance that one would have expected, there were some premature beats and for a short time once there was auricular fibrillation. The *Q–R–S* deflections were usually larger than normal, suggesting congenital heart disease. *P*2 and *P*3 often suggested auricular hypertrophy. Figure 3 shows ventricular asynchronism. As Petit[8] puts it, the two ventricles do not contract simultaneously. The *Q–R–S* presents successively the characteristic predominance of one or the other ventricle and takes on a diphasic aspect. In the *Q–R–S* of Figure 3, in the first phase there is a deep *Q*1 and a tall *R*3 as in predominance of the right ventricle. In the second phase there is a tall *R*1 and a deep *S*3, the sign of a left ventricular preponderance. He thinks that the succession of the two predominances can only be explained by ventricular asynchronism, in this case the right predominance preceding. The exaggerated hypertrophy of the right ventricle makes this easy to understand. The electrocardiogram confirms the clinical findings of a doubled first sound at the apex at times.

Discussion. The first impression of everyone on examining the patient was that mitral stenosis was a part of the picture. The short, sharp, exaggerated first sound, the diastolic murmur at the apex, the exaggerated pulmonary second with the very marked diastolic murmur at the pulmonary cartilage suggested a mitral stenosis with a Graham-Steell murmur of pulmonary insufficiency. Real congenital mitral stenosis is rare,[9] and in a cyanotic subject is apt to be associated with patent ductus arteriosus which we felt sure we did not have in this case.

The cases of mitral stenosis with interauricular defect of Lutembacher[10] did not help because in this condition cyanosis is usually late.

The early and high degree of cyanosis and the comparative frequency of tetralogy of Fallot as the underlying cause made a better prospect. The prominence of the right ventricle and of the pulmonary segment, especially in the Roentgen ray picture, suggesting interventricular defect and pulmonary stenosis were helpful. The lack of a constant systolic murmur at the pulmonary cartilage and the constant presence of a diastolic murmur there, made us feel that pulmonary insufficiency was sure and that pulmonary stenosis was absent or of a very mild degree.

Any broadening of the aortic shadow to the right of the median line was not found, though of course we did not suspect hypoplasia of the aorta. Dr. Fowler's report of the postmortem shows that the diagnosis of tetralogy of Fallot was confirmed, but in addition there was the unexpected hypoplasia of the aorta.

Postmortem Examination. The postmortem examination presented a well developed and well nourished white female of 31. The skin showed

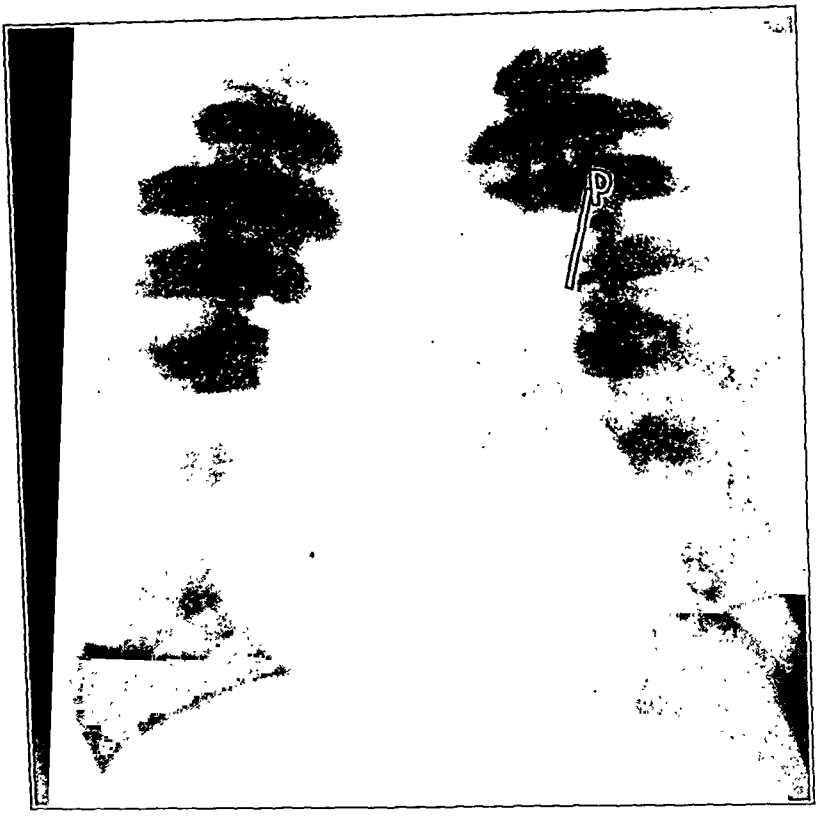


FIG. 1.—Silhouette (6 feet) of heart and great vessels, showing great prominence of pulmonary arc (*P*), a wide transverse diameter, an enlarged right ventricle, and globular shape of ventricles.

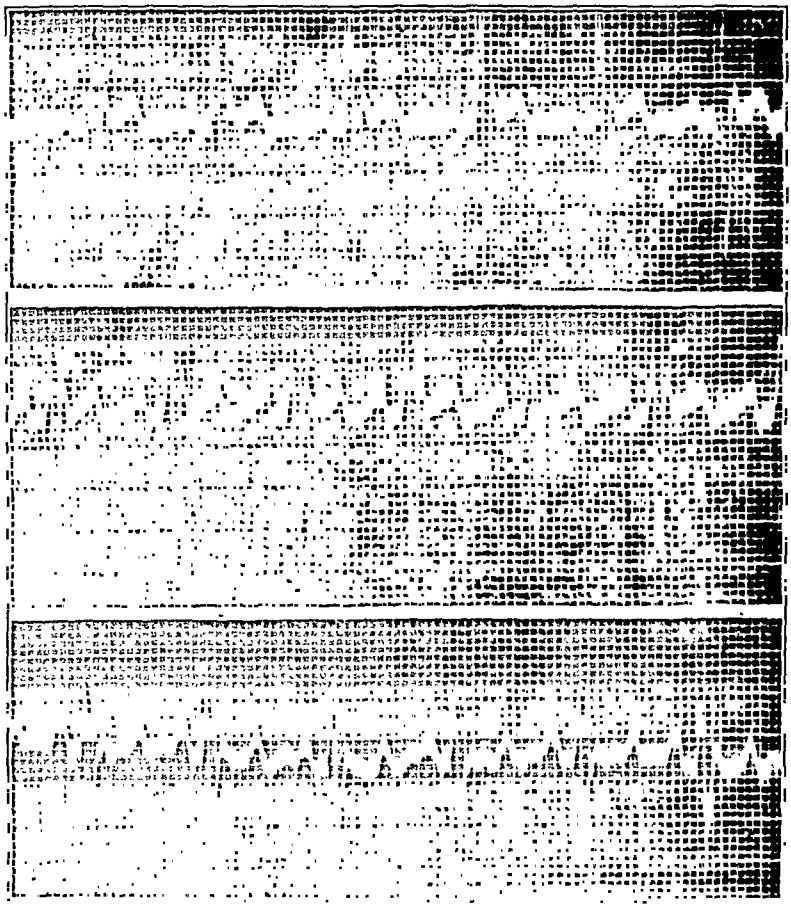


FIG. 2.—Taken December 6, 1928. This is a fair sample of the average curve. The amplitude of *Q–R–S* in Leads I and II suggests congenital heart disease. *P2* and *P3* are quite prominent.

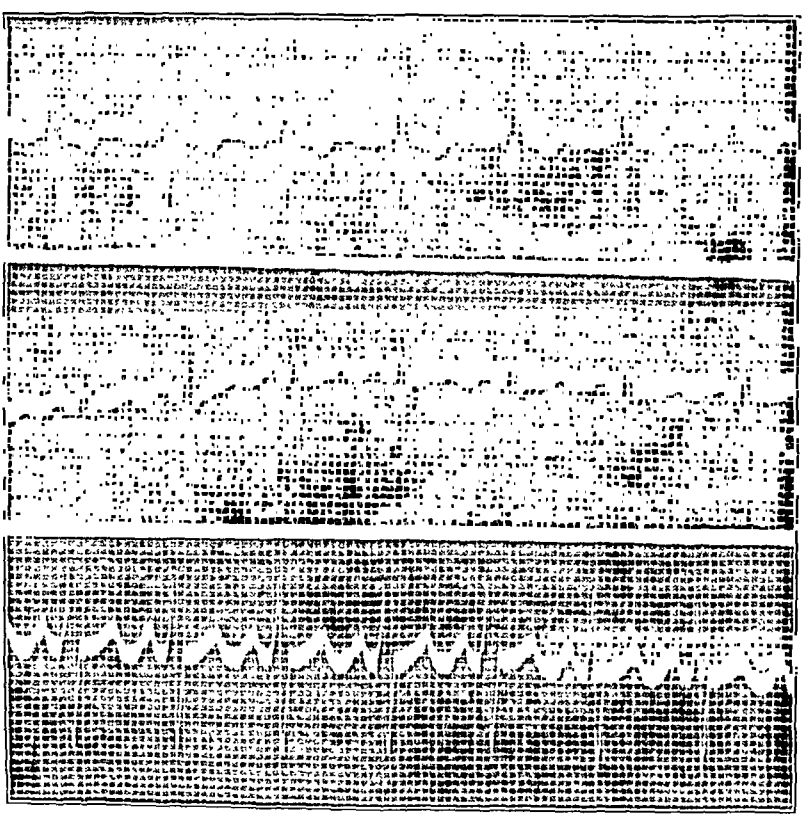


FIG. 3.—Taken February 7, 1929. Shows ventricular asynchronism.

a dusky cyanosis. The fingers were markedly clubbed. Half a liter of clear fluid was found in the left pleural cavity. The lungs were wet and congested.

The pericardial cavity contained 350 cc. of bloody fluid. The transverse diameter of the heart was 15 cm. The heart was globular in shape, the apex being formed by the right ventricle (Fig. 4). The weight was 500 gm.

There was dilatation and hypertrophy of the right ventricle. The wall of the right ventricle was 1.5 cm. thick. The conus arteriosus was slightly widened and markedly thickened. The pulmonary orifice measured 10 cm. in circumference (Fig. 5). The pulmonary cusps were thickened, of unequal length, and the margins were rounded. The left anterior one was fused with the posterior one. The right anterior cusp was voluminous. There



FIG. 4.—Heart showing globular shape, transposition and hypoplasia of aorta (*A*), and dilated pulmonary artery (*PA*).

was a fusiform dilatation of the pulmonary artery, the greatest circumference of which was 10.5 cm., and there was a moderate atherosclerosis. There was a ragged tear 3 cm. in length in the intima of the pulmonary artery just above the orifice. Blood had extravasated into the media and adventitia.

The left ventricle was dilated, but not to the extent seen in the right ventricle. The wall was hypertrophied, measuring 3 cm. in thickness. The aorta appeared displaced to the right and somewhat rotated on its axis so that it overrode an interventricular defect 2.5 by 2 cm. in the anterior portion of the pars membranacea septi (Figs. 5 and 6). The interventricular septum measured 2 cm. at its thickest part.

There was marked hypoplasia of the aorta. The circumference of the aortic ring was 5.5 cm. The greatest circumference of the arch was 4.5 cm.

and of the thoracic aorta 3 cm. The aortic cusps appeared normal, the lining smooth.

The leaflets of the mitral and tricuspid valves were normal except for a slight thickening. The rings of these valves were 12 and 13 cm. in circumference respectively. The atria showed no remarkable features.

The *liver* was enlarged and weighed 2100 gm. On section the parenchyma was wet and a dark red color. There was marked dilatation of the veins and arteries throughout the parenchyma of the liver.

The *gall bladder* appeared normal.

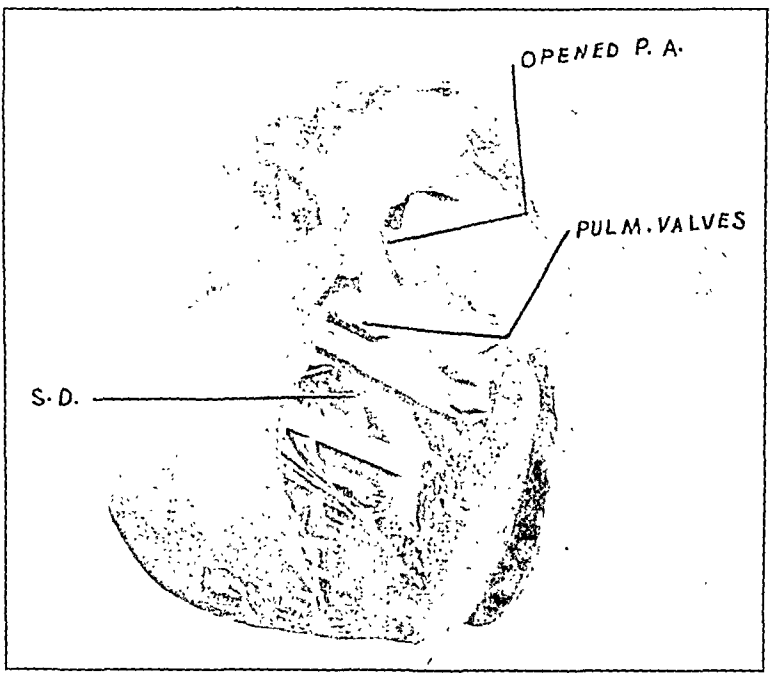


FIG. 5.—Opened right ventricle, showing hypertrophy of wall, scarring of pulmonary leaflets, marked widening of opened pulmonary artery (*Opened P.A.*) and septal defect (*S.D.*).

The *spleen* was enlarged and weighed 250 gm. The capsule was tense and stretched. On section there was seen an infarct on the diaphragmatic surface of the spleen. Parenchyma was firm and a dark red color.

The *pancreas* grossly appeared normal.

The *kidneys* weighed 350 gm. together. Their capsules stripped off with ease. On section the cortex was of normal thickness and a pale red color. The calyces and pelves were normal.

The *uterus* and *adnexa* showed no unusual features.

The *urinary bladder* was empty.

Examination of the *gastro-intestinal tract* showed no pathologic condition.

Microscopic Examination. Lungs. Sections show many of the alveoli filled with blood, heart failure cells and fluid. Some sections show a considerable increase in the interstitial connective tissue. The bloodvessels throughout the parenchyma are dilated.

Heart. Sections through the right and left ventricles show the nuclei of the muscle fibers to be larger than normal. There is some increase in

connective tissue throughout the myocardium. There are a few focal areas of lymphocytic cell infiltration scattered throughout the myocardium.

Pulmonary Artery. The media is composed of a rather hyalinized connective tissue. The adventitia is infiltrated with extravasated blood.

Aorta. Gross sections show no unusual features except the aorta is considerably less than normal thickness.

Liver. There is a marked dilatation of the central veins and arteries. The hepatic sinuses surrounding the central veins are dilated. The hepatic cells appear atrophic in character.

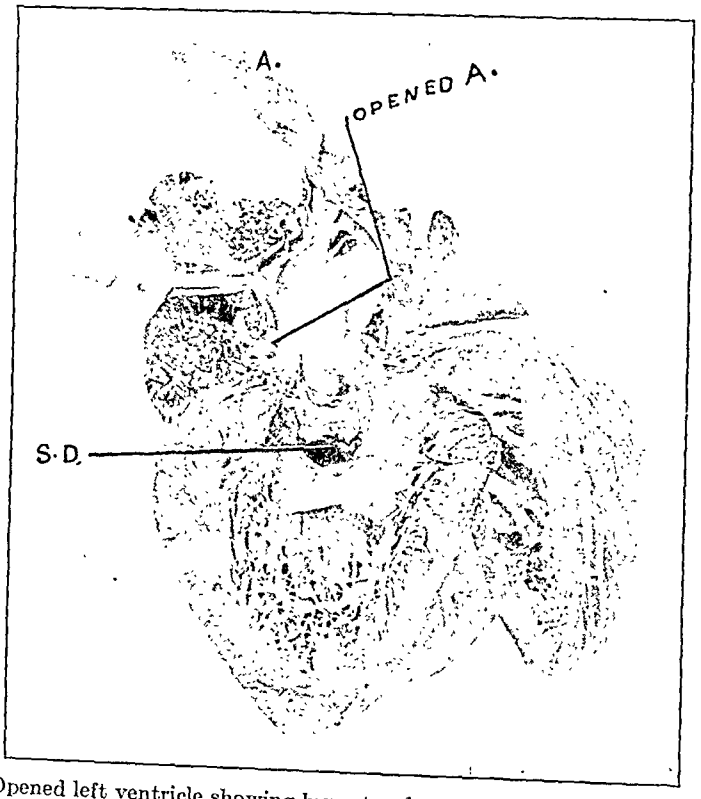


FIG. 6.—Opened left ventricle showing hypertrophy of wall, septal defect (*S.D.*) and opened hypoplastic aorta (*Opened A.*).

Spleen. Sections through the infarct show degeneration and necrosis of the splenic pulp. The adjacent parenchyma shows marked congestion of the pulp.

Kidney. The glomeruli diffusely throughout the sections appear large, cellular and congested. The bloodvessels throughout the cortex and medulla are dilated. There is slight tubular degeneration.

Pancreas. Sections show no marked changes from normal.

Adrenal. There is slight hydropic degeneration of the cortex.

Summary. The patient, a woman a little over 31 when she died, was born at 8 months and was a "blue baby." She had a normal physical and mental development, passed through two pregnancies and was able to take care of her house until within a month of her

death. The diagnosis of tetralogy of Fallot, with the incompetency of the pulmonary valves was confirmed at postmortem. In addition there was a hypoplasia of both the thoracic and abdominal aorta, which was not suspected.

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COARCTATION OF THE AORTA WITH INTERMITTENT LEAKAGE OF A CONGENITAL CEREBRAL ANEURYSM.

Report of a Case.

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Coarctation of the aorta implies a partial or complete occlusion of the lumen of the aorta and when it affects an adult, it occurs at or near the insertion of the ductus arteriosus, which is usually just distal to the origin of the left subclavian artery. Blackford found that, in a series of 68,300 consecutive necropsies reported by 6 authors, coarctation of the adult type occurred 43 times or an incidence of 1 in 1588 necropsies. Less than 350 reports of this anomaly are to be found in the literature, and the condition was diagnosed clinically in less than a fourth of these cases. These statistics clearly indicate that coarctation of the aorta exists far more frequently

than is clinically appreciated. However, there has been a very noticeable increase in the number of cases reported within the past 5 years.

The etiology and pathogenesis of this condition have been adequately reviewed by Abbott and by Blackford, and need not be considered here. Congdon has added much to the understanding of the pathogenesis of cardiovascular anomalies by his contribution on the embryologic development of the aortic-arch system.

Bonnet has divided coarctation of the aorta into the infantile and adult types. The infantile type is merely a narrowing of the isthmus of the aorta and may be considered as a persistence of the anatomic relations that existed under the conditions of fetal circulation. This type has little clinical significance as the victims are all doomed to an early death.

In the adult type, a pathologic condition is found which has no counterpart in intrauterine existence. The findings which are usually quite typical are well illustrated in Fig. 1. This specimen was obtained at necropsy of a case observed by one of us (Shelden). This case previously was included in the series collected by Blackford. The aorta appears as though it had been ligated at the point of constriction. An hour-glass bulge is usually present above and below the constriction, and the ascending portion may be the seat of an aneurysmal sac. Occasionally, the aorta may be hypoplastic throughout. Cardiac hypertrophy occurs in 75% of the cases (Blackford), and bicuspid aortic valve is present in 25% of cases (Abbott). Other anomalies of the great vessels of the aorta and of the cerebral vessels are frequently encountered. The innominate and subclavian arteries and their branches, together with the arteries which are usually responsible for collateral circulation, namely the first three intercostal, the dorsalis scapular, the internal mammary, and the deep epigastric arteries, are markedly dilated in most cases. Other arteries may assist in collateral circulation.

Diagnosis. The diagnosis is not a difficult one, and is not dependent on laboratory or roentgenographic confirmation, although the latter is frequently helpful. In the great majority of cases the patients are robust young adults who have led an active life and frequently have participated in athletics. The latter observation has been attributed by some writers to the increased cerebral circulation. Because of the paucity of symptoms, the physician is frequently not consulted until the signs of cardiac insufficiency or an unexplained cerebral hemorrhage has occurred. The seriousness of the complication may make a thorough examination impractical so that coarctation of the aorta may not be recognized as the contributing factor. Intermittent claudication or "poor circulation" is occasionally the presenting complaint.

The signs of coarctation of the aorta are quite definite and once the diagnostic features are discovered, the clinical diagnosis is

almost always substantiated by necropsy. The cardial signs may be summarized as follows:

1. A forceful, bounding pulse is noted in the vessels of the neck and upper extremities, and an absence or marked diminution of pulsation, in the vessels of the lower extremities. If a feeble pulse is detected over the femoral arteries, it is asynchronous with the radial pulse.

2. A palpable aortic pulsation is absent in the abdomen whereas a forceful systolic thrust is present in the suprasternal notch.

3. There is hypertension in the brachial arteries, usually with a definite pulse pressure and a much lower blood pressure in both popliteal arteries. This is a reversal of the normal state.

4. Evidence of a well-developed collateral circulation is found. Large, tortuous, anastomosing arteries may be seen and palpated in the interscapular, suprascapular, and axillary regions, and less often are conspicuous over the anterior aspect of the thorax. The internal mammary and deep epigastric arteries are occasionally visible and palpable. These collateral vessels transmit a systolic or presystolic murmur and frequently a fine accompanying thrill.

5. A murmur, which is usually heard over the aortic area, has its maximum intensity along the left border of the sternum. This murmur is frequently altered by the congenital or acquired valvular lesions which may be present. Cardiac hypertrophy is present in three-fourths of the cases.

While the diagnosis is essentially a clinical one, certain accessory roentgenologic signs are of value when present. They are as follows: (1) a bilateral erosion of the inferior borders of the ribs; (2) an absence of the prominent aortic knob, usually associated with hypertension; and (3) a dimpling of the descending aorta, which is best seen in the left oblique position.

Association of Cerebral Aneurysms With Coarctation. The frequency with which cardiovascular anomalies, such as a bicuspid aortic valve, defects of the aortic septum, subaortic stenosis, persistent left superior vena cava, anomalous origin of the arteries from the aortic arch, and congenital cerebral aneurysms, are associated with coarctation would almost appear to be a significant part of the picture. Of these associated anomalies, only the cerebral aneurysm presents a grave source of potential danger.

Eppinger, in 1887, first suggested rupture of a congenital aneurysm of the cerebral arteries as an explanation of cerebral hemorrhage of unknown etiology, particularly in young adults. He says that "in the small and smallest arteries, like those forming the circle of Willis and its branches, many aneurysms have a congenital origin and are due to an inborn defect of the arterial wall." Many observers have since reached the same conclusion, and it is generally agreed that rupture of a congenital cerebral aneurysm must be considered as an explanation in any "spontaneous" cerebral or meningeal

hemorrhage which affects a non-hypertensive individual, particularly a young person. Except in rare instances, these small aneurysms are not dependent on infection. Fearnsides reported that only 6% of the aneurysms of the small cerebral arteries can be proved to have a possible syphilitic basis, and these largely occur in the basilar and vertebral arteries. Aneurysms of the cerebral vessels, which are of syphilitic origin, usually attain sufficient size to produce symptoms that simulate tumor of the brain, while the aneurysms of congenital origin are often very small and usually do not give rise to symptoms until intermittent leakage or rupture occurs. Forbus and others in studying these congenital cerebral aneurysms found an absence of the media of the arterial wall at the bifurcation of the cerebral vessels from the circle of Willis, where the great majority of these aneurysms are found. Forbus also demonstrated that a greater pressure is exerted on the arterial wall at the angle of bifurcation than elsewhere. It is, therefore, not surprising that, in cases of coarctation of the aorta in which there has been a sustained hypertension in the cerebral vessels since early life, we should frequently find these congenital aneurysms, and that "spontaneous" cerebral or meningeal hemorrhage is the cause of death in a relatively high percentage of these cases.

Woltman and Shelden found that in 32 cases of coarctation of the aorta with neurologic complaints, in which necropsy was performed, cerebral hemorrhage was responsible for death in 37.5%. This complication was also found to be the cause of death in 17% of the cases in the series collected by Blackford. Abbott, in 1928, collected the reports of 20 cases of coarctation of the aorta, in which cerebral hemorrhage was the cause of death. In 7 of these cases, a ruptured congenital aneurysm was definitely demonstrated to be the source of hemorrhage. She said: "In view of the extreme difficulty and sometimes the impossibility of locating these very small, almost miliary aneurysms, on the cerebral vessels in the midst of a large hemorrhage at the base, and the extreme youth of most of the patients so dying in this series, it seems safe to conclude the presence of a ruptured cerebral aneurysm in practically all such cases of so-called spontaneous cerebral hemorrhage occurring in coarctation before the end of the second decade without a history of infection or other apparent cause."

Eppinger (1887), Kolisko (1913), Strassmann (1922), Woltman and Shelden (1927), Parkes Weber (1927), and Green (1928) have reported cases of coarctation of the aorta in which necropsy revealed that the spontaneous cerebral hemorrhage was clearly the result of a ruptured aneurysm of the cerebral vessels.

Parker, in 1926, emphasized the phenomenon of "intermittent leakage" as a diagnostic sign of a small rupture in the aneurysmal sac, in which the small, slitlike aperture closes following a certain amount of bleeding. He said: "Much more interesting clinically

are the cases of intermittent leakage of blood from the aneurysmal sac with alternating episodes of disturbed function and periods of relatively good health. . . . In these cases, there was a history of two, three, or more apoplectiform seizures separated by varying intervals. At necropsy the pathologic counterpart of these episodes was found in different layers of old and recent hemorrhage from a ruptured aneurysm at the base of the brain. This general behavior is characteristic and diagnostic in a large percentage of cases of intracranial aneurysms and makes it possible to recognize the disease during life. The onset of these attacks is usually sudden and associated with sudden severe headache or sensation of something giving away in the head."

Lichtenberg and Gallagher have reported the only case of coarctation of the aorta associated with intermittent leakage of a cerebral aneurysm diagnosed during life. Their patient, who was a girl, aged 12, was still living 18 months after the cerebral accident. It is our purpose to record a similar case in which the association of these two anomalies has been diagnosed during life.

Case Report. *History.* A married woman, aged 25, came to the clinic on April 17, 1935, complaining of a recent diplopia and hypertension. Prior to July, 1934, she had always enjoyed exceedingly good health and had indulged strenuously in tennis, hockey, basketball, and swimming. Pertussis was the only illness which the patient recalled with the exception of a traumatic injury to the back, which had occurred in 1933. There was no history of rheumatic fever or syphilis and she knew of no other cases of hypertension in the family.

In July, 1934, after swimming for almost 2 hours, she had experienced a "sudden, bursting sensation in the head," which had been followed immediately by a violent headache over the right temporal region, blurred vision, vertigo, and generalized weakness. She had not lost consciousness. She said that she would have drowned if the occupants of the accompanying boat had not seen her plight and pulled her from the water. The headache and vertigo had persisted for 2 hours. She had consulted her physician a few days later, at which time the value for her systolic blood pressure had been found to be 185 mm. of mercury. This had been the first knowledge of her hypertension.

She had then felt perfectly well until March 15, 1935, when a severe, throbbing, pulsating headache had developed. This had been localized over the right temporofrontal area. The headache had been present almost constantly for 2 weeks; it usually had been accompanied by dizziness, nausea, and occasionally by blurred vision. The value for the blood pressure was found to range as high as 220 mm. of mercury at this time.

On April 8, 1935, she had experienced a syncopal attack, which had been preceded by a sudden loud noise in the head and a severe pulsating headache. The syncope had lasted less than 5 minutes and so far as the patient was aware, it had been unaccompanied by any significant features.

On April 13, 1935, while purchasing a few articles at a drug store she suddenly had lost all vision in the right eye. This attack also had been followed by severe headache and dizziness but there had not been any hemiplegia, loss of consciousness, disturbances of speech, paresthesia, and so forth. She had noticed some return of vision after 3 hours, and 4 days later the vision had been found to be normal. Diplopia, dilatation

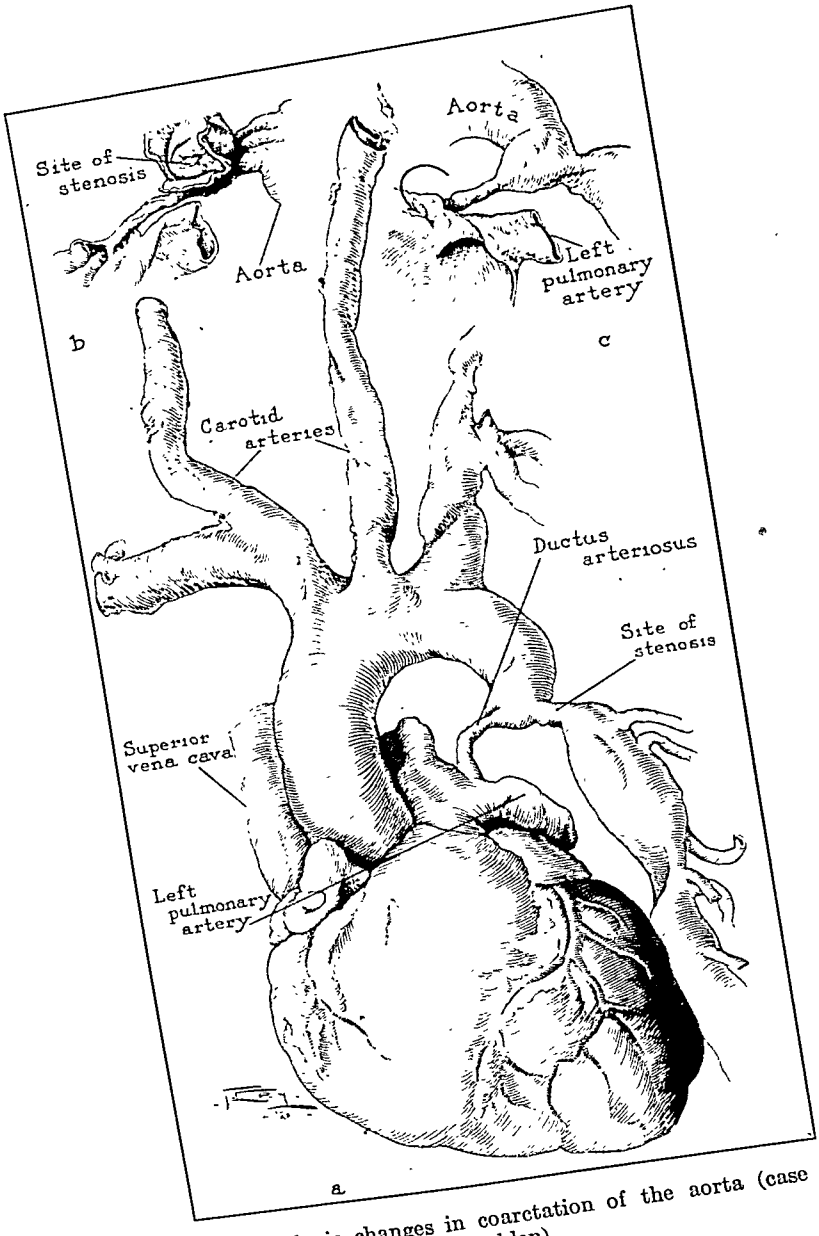


FIG. 1.—Gross pathologic changes in coarctation of the aorta (case observed by Shelden).

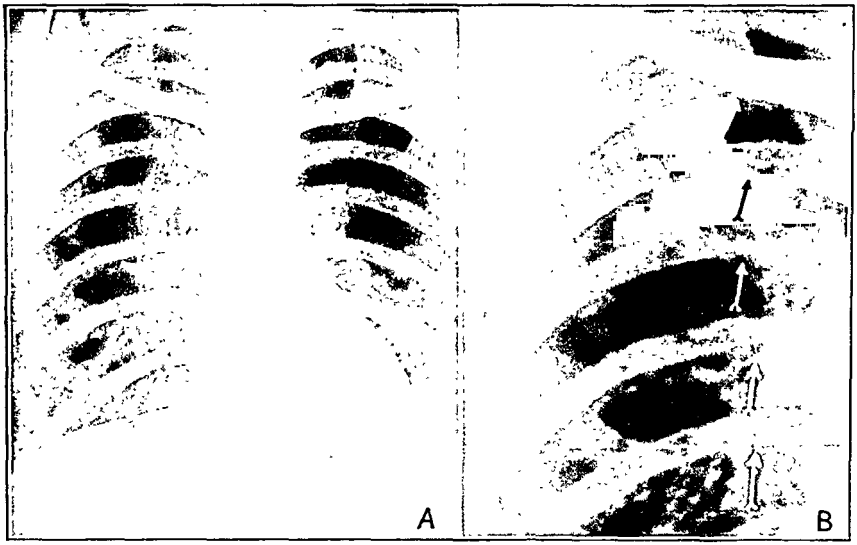


FIG. 2.—*A*, Bilateral erosion of the ribs posteriorly, absence of the shadow of the aortic knob and normal cardiac shadow in the case reported; *B*, arrows indicate areas of erosion of ribs produced by dilated intercostal arteries.

of the right pupil, and slight ptosis of the right lid had been noticed with the return of vision. She came to the clinic 4 days after this episode.

Physical examination revealed a young woman, who was well developed and of an athletic build and who weighed 136 pounds (61.7 kg.). The lungs, abdomen, and pelvis were essentially normal. The tonsils were large and cryptic but not obviously diseased. The thyroid gland was moderately full. The pulse and temperature were normal.

The heart was apparently not enlarged, but auscultation revealed a well-defined double murmur over the aortic valve, with its maximal intensity transmitted along the left border of the sternum. The radial pulse in each arm was forceful, sudden, relapsing, and of the Corrigan type. The value for the systolic blood pressure in the right arm was 182 mm. of mercury and that for the diastolic was 82 mm. of mercury, revealing the high pulse pressure of aortic insufficiency. A slight capillary pulse in the nail beds was present. In attempting to elicit the Duroziez "pistol-shot" sound over the femoral arteries, the clue to the correct diagnosis was found. There were no pulsations over either femoral artery. This was substantiated by totally absent pulsations of the posterior tibial, dorsalis pedis, and popliteal arteries in both legs, but because of an apparently adequate collateral circulation, there was no pallor of the lower extremities with elevation, or rubor with dependency. There was likewise no palpable pulsation of the abdominal aorta although the vertebral column could be palpated with ease. The pulse in the carotid, brachial, ulnar, and radial arteries was full and bounding.

The blood pressure was taken in the recumbent position and the values in millimeters of mercury were as follows: for the right brachial artery: systolic 182, diastolic 82; for the left brachial artery: systolic 176, diastolic 74; for the right popliteal artery: systolic 118, diastolic ?; for the left popliteal artery: systolic 128, diastolic ?. The sounds were heard with difficulty over the popliteal vessels and the oscillations of the manometer were barely perceptible.

No visible pulsating vessels over the thorax were observed. There were, however, several palpable vessels in the interscapular regions of both sides and the murmur could be heard over all of the upper intercostal arteries and over the dorsalis scapular arteries in the axillary and posterior aspects of the thorax.

Neurologic Examination. On the right side there was a ptosis of the upper lid, a paralysis of the internal rectus muscle, a loss of convergence, and a dilatation of the pupil, indicating a partial paralysis of the oculomotor nerve on the right side.* Reflexes were bilaterally exaggerated but equal. No pathologic reflexes were present. Vision was normal in both eyes and the visual fields were roughly normal. The ocular fundi showed only a slight hypertensive diminution in the caliber of the arteries.

Laboratory Data. The Kline and Kahn reactions of the blood were negative. The hemoglobin, blood count, amount of urea in the blood, and the urine were all normal. A blood culture did not show any growth on blood and brain agar within 48 hours.

Roentgenographic Examination. A roentgenogram of the thorax revealed a bilateral erosion of the inferior surfaces of the 4th, 5th, 6th, 7th, and 8th ribs posteriorly; the erosion was more pronounced on the right side than it was on the left. The aortic knob was not visualized and there was no cardiac hypertrophy (Figs. 2A and B). A roentgenogram of the head did not reveal any abnormality. Unfortunately, a left oblique roentgenogram of the thorax was not made as it was necessary for the patient to return home before this could be done. An examination of the cerebrospinal fluid was omitted for the same reason.

* Correspondence has revealed that the diplopia persisted for a period of 2 months.

Comment. Although frequently overlooked, as the incidence in a large number of necropsies indicates, coarctation of the aorta produces outspoken clinical signs and the diagnosis is not difficult. It requires only a routine palpation of the aorta and the peripheral vessels, a few readings of the blood pressure, and a threshold of suspicion which includes this interesting anomaly as a possibility in any unexplained cardiovascular disease or accident which affects a young adult. In any case in which a patient who is less than 40 years presents signs of cardiac insufficiency without a rheumatic or syphilitic basis, coarctation should be considered. Routine palpation of the peripheral vessels and readings of the blood pressure in the popliteal arteries occasionally will reveal coarctation of the aorta which has masqueraded previously under the diagnosis of essential hypertension. The possibility of coarctation should be borne in mind when the patient complains of intermittent claudication, although the great majority of these patients will have thromboangiitis obliterans or arteriosclerosis obliterans.

Once the diagnosis of coarctation of the aorta is established, any cerebrovascular accident should suggest the possibility of an intermittent leakage or rupture of a congenital cerebral aneurysm, most frequently situated in the circle of Willis, as the association of these two anomalies is not infrequently observed. In the case here presented, it was the neurologic lesion which first called attention to the aortic anomaly. We feel that this patient had suffered two and possibly three episodes of intermittent leakage of a cerebral aneurysm without an actual rupture in the strict sense of the word. She returned home with the advice to discontinue athletics and to avoid strenuous physical activities in the hope of preventing a vascular catastrophe.

Abbott has shown that in 77% of these cases death was the result of coarctation or one of its complications. These complications include rupture of the heart or of the ascending portion of the aorta (20%), cardiac insufficiency (30%), cerebral hemorrhage (12%) mycotic endarteritis and rupture of mycotic aneurysms just below the coarctation (7%), and cardiac asystole without apparent cause (8%). The average span of life is approximately 35 years. By recognizing this anomaly early, much can be done to avert disaster by curtailing physical activities and prohibiting athletics in which, strangely enough, most of these patients strenuously indulge.

Summary. A series of an unusually large number of consecutive necropsies indicates that coarctation of the aorta occurs far more frequently than is clinically appreciated. The pathology and diagnosis of this anomaly is discussed and attention is called to the ease with which this diagnosis may be confirmed or denied. The association of congenital cerebral aneurysm with coarctation is emphasized. A case in which coarctation with possible intermittent leakage of a congenital cerebral aneurysm affected a young woman still living is reported.

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PRIMARY PULMONARY ARTERIOSCLEROSIS WITH POLYCYTHEMIA: ASSOCIATED WITH THE CHRONIC INGESTION OF ABNORMALLY LARGE QUANTITIES OF SODIUM CHLORID (HALOPHAGIA).

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A growing interest in the subject of pulmonary arteriosclerosis has centered in the observation that the phenomenon is apparently the usual, if not the invariable, result of a prolonged elevation of

pressure in the pulmonary circulation. With few exceptions this hypertension has been due to extravascular obstruction to the pulmonary circulation producing what we may call the "syndrome of obstruction" in the lesser circulation—dyspnea, cyanosis, polycythemia and right ventricular hypertrophy. The majority of cases presenting this syndrome reveal an antecedent and probably related cardiac, bronchial or pulmonary abnormality, but there are instances in which such a causative factor is not demonstrable.

The case herewith presented is one which shows extensive sclerosis of the smaller pulmonary arteries. The symptoms of lesser circulatory obstruction were prominent during life. The rôle played by an abnormal appetite for and lifelong ingestion of excessively large quantities of sodium chlorid is questionable. Following a brief discussion of the pathologic changes involved, the clinical features of our case will be considered from two standpoints: first, those which are chiefly of interest in relation to diagnosis, and second, those which are of interest in relation to etiology.

Case History. A young woman, aged 20, was first seen in December, 1932, complaining of marked shortness of breath, "pounding of the heart" upon the slightest exertion and an almost constant craving for salt—all present since early childhood; and of more recent origin, vaginal bleeding and inability to sleep.

The patient's parents state that when she was 3 weeks old a definite blueness of the lips was observed but that no other abnormality in the child was noted until she became large enough to climb into a chair and reach objects on a table or sideboard. It was then that an abnormal hunger for salt became manifest and the knowledge of certain punishment would not deter her from appropriating the contents of a salt tumbler. When about 4 years old it was noted that shortness of breath and exhaustion were beginning to prevent the patient from indulging in activities usual to children of that age.

During childhood the patient had pneumonia 6 times, the first attack occurring at 2 years. The susceptibility to frequent respiratory infections was not relieved by tonsillectomy at 12. She never suffered from a chronic cough nor was there ever any suggestion of asthma. When she was 15 she was placed in a girl's school where a positive blood Wassermann was reported to have been found. She was given 3 doses each of mercury and arsenic, then taken home and placed under the care of a dermatologist who could not, however, verify the diagnosis of syphilis. No more treatment was given and blood Wassermann tests continued to be consistently negative at yearly intervals.

In October, 1931, the patient came to the Rocky Mountain region and was married. She had spent her life near sea level and on coming to the higher altitude she noted a marked aggravation of the respiratory distress. In May, 1932, she induced the miscarriage of a 3½ months' fetus following which uterine bleeding persisted until a curettement was done early in December, 1932, by Dr. C. A. Dorsey, who subsequently referred her to one of us (W. D.) for study.

When she was first seen, a short walk was sufficient to induce extreme fatigue with marked dyspnea. For more than a year sleeping had been difficult because of inability to breathe freely on lying down. She stated that she was eating as much as from 2 to 3 pounds of salt a week and that she always carried rock salt with her to consume between meals.

Physical Examination and Laboratory Findings. The patient was a well developed, young adult female, with moderate cyanosis of the skin of the face and extremities. There was no clubbing of the fingers or toes. Microscopic examination revealed the skin capillaries at the nail root to be elongated, tortuous and dilated throughout the arterial limb. The eye grounds were a deeper red color than normal, with marked dilatation and tortuosity of the retinal veins. The nasal and pharyngeal mucous membranes were markedly cyanotic. The tonsils were absent. The breasts were large and pendulous, extending below the umbilicus. The thorax was of normal configuration. Examination of the lungs revealed no abnormalities to percussion or auscultation. No thrills could be palpated over the precordial area. Percussion of the heart borders revealed moderate enlargement to the right in the fifth interspace and marked enlargement to the left at the base. The heart sounds were labored and a marked reduplication and accentuation of the pulmonic second sound was found. No murmurs could be heard. Tenderness was present in the left lower abdominal quadrant and on pelvic examination a small mass was found in the left adnexal region. The pulse was 86, respiratory rate 30, temperature 98° and weight 132 pounds. Blood pressures taken on 3 different occasions were: 108/90, 110/90 and 112/96.

Roentgen Ray Study of the Chest (Drs. F. B. Stephenson and K. D. A. Allen). The fluoroscopic examination revealed a bulging in the region of the pulmonary artery in which pulsations corresponded with ventricular systole; the excursion of both diaphragms was good. The roentgenograms of the chest showed a marked enlargement of the pulmonic arch, enlargement of the right ventricle and right auricle, and extensive fibrosis in the hilar regions and bronchial system. A comparison of the heart shadows in systole and diastole revealed increased width of the right heart in all phases and a failure of the heart to exhibit a normal range of change between diastole and systole, the right side of the heart showing only about half as much change as the left side when radiated in the two phases (Figs. 1 and 2*).

The electrocardiographic tracing showed the changes peculiar to right ventricular preponderance.

The average vital capacity was 2650 cc., and tidal air 700 cc. (Narragansett Wet Spirometer). This vital capacity was within normal limits for this patient but the tidal air was considerably above normal.

Nothing abnormal was found in the urine.

A fractional gastric analysis gave results within normal limits. A barium Roentgen ray series revealed no gastro-intestinal abnormalities save a spastic colon.

Blood chemistry studies gave normal findings as to dextrose, total nonprotein nitrogen and urea nitrogen. The bleeding and coagulation times were normal. The globulin and albumin respectively were 3 and 5.2 gm. per 100 cc. of serum. The blood serum osmotic pressure was 360. These determinations were all within normal limits. The hemocytologic findings are incorporated in Table 1. An increased level of hemoglobin and a moderate polycythemia were found.

Clinical Course and Subsequent Observations. During the first 7 days' observation this patient consumed 34 ounces of salt. She refused to go for more than 4 days without salt. Between the dates of December 12, 1932, and January 20, 1933, she was given 2 gm. of phenylhydrazin hydrochlorid which resulted in no alteration of the blood findings. On January 23, a small hemorrhoid was removed following which the patient hemorrhaged for 1 week, the red count dropping to 5,650,000 by January 31. On February 3 she entered the Colorado General Hospital where ad-

* The measurements noted are according to the careful work of Levene and Reid.[1]

ditional blood studies were made by Drs. E. R. Mugrage and R. H. Hill. Hemoglobin determinations from the same specimen of blood were made and the grams per 100 cc. of blood with each method used were as follows: 18.58, Van Slyke; 18.81, Wong; 19.50, Osgood-Haskins. The red count on this day was 6,265,000. The Kahn, Müller, Wassermann and Hinton tests for syphilis were all negative. Blood volume studies by the use of intravenous brilliant vital red were made. The results compared with the theoretical normals are as follows:

	Patient.	Normal.
Plasma volume	2669 cc.	2969 cc.
Whole blood volume	6221 cc.	4640 cc.
Plasma volume per kg.	46 cc.	51 cc.
Whole blood volume per kg.	107 cc.	80 cc.
Plasma volume, %	42.9	64
Cell volume, %	57.1	36

The red count on this day was 6,930,000.

On March 31 the patient returned to her home in Columbus where she reported for observation on April 6, 1933.

After her return to near sea level it was found that the red count decreased appreciably (Table 1). The Wassermann and Kahn tests were again found to be negative. Hemolysis began at a salt equivalent concentration of 0.430 and was complete at 0.267 (Wiseman technique[2]) showing increased erythrocyte resistance. The following additional data were obtained on the dates indicated.

Date.	4/6.	4/12.	4/18.	Comparison with normal.
Cell volume, %	58	59	58	High
Mean corpuscular volume	92	120	118	Normal to high
Mean corpuscular hemoglobin	22	28	32	Low to normal
Mean corpuscular hemoglobin concentration	24	22	27	Low
Sedimentation rate	10	0	2	Normal
Icteric index	10	15	15	High

The basal metabolic rate was +5.

Studies directed toward the investigation of the abnormal salt intake were of considerable interest. Dr. S. Renshaw, in a careful study of her gustatory stimulus limens for sodium chlorid (that concentration of salt barely appreciable to taste), found her salt threshold to be strikingly low compared to "normal" individuals. Space does not permit the elaboration of the technical details necessary to make accurately such an observation. Briefly, the threshold for a given substance (sodium chlorid in this case) at a given temperature is determined by a method of linear interpolation after plotting the percentage of positive judgments against the corresponding solution strengths. A judgment is considered positive when the subject is able to differentiate between distilled water and the test solution. Table 2 gives the percentage of positive judgments made by our patient for various concentrations of sodium chlorid at temperatures ranging from 3° to 47° C. The figures at the bottom of the table are the values of the thresholds at these temperatures and are interpreted as fractions of a 1% solution by weight. In order to give some notion of the patient's sensitivity to the taste of salt, Fig. 3 compares her thresholds with those of individuals who were normal with respect to taste and salt intake.

Table 3 contains data relating to the daily fluid intake, urinary output, salt intake, urinary chlorid and blood chlorid. Data taken when the patient was allowed to ingest sodium chlorid in any amount is compared with that taken when no salt was permitted (Fig. 4).

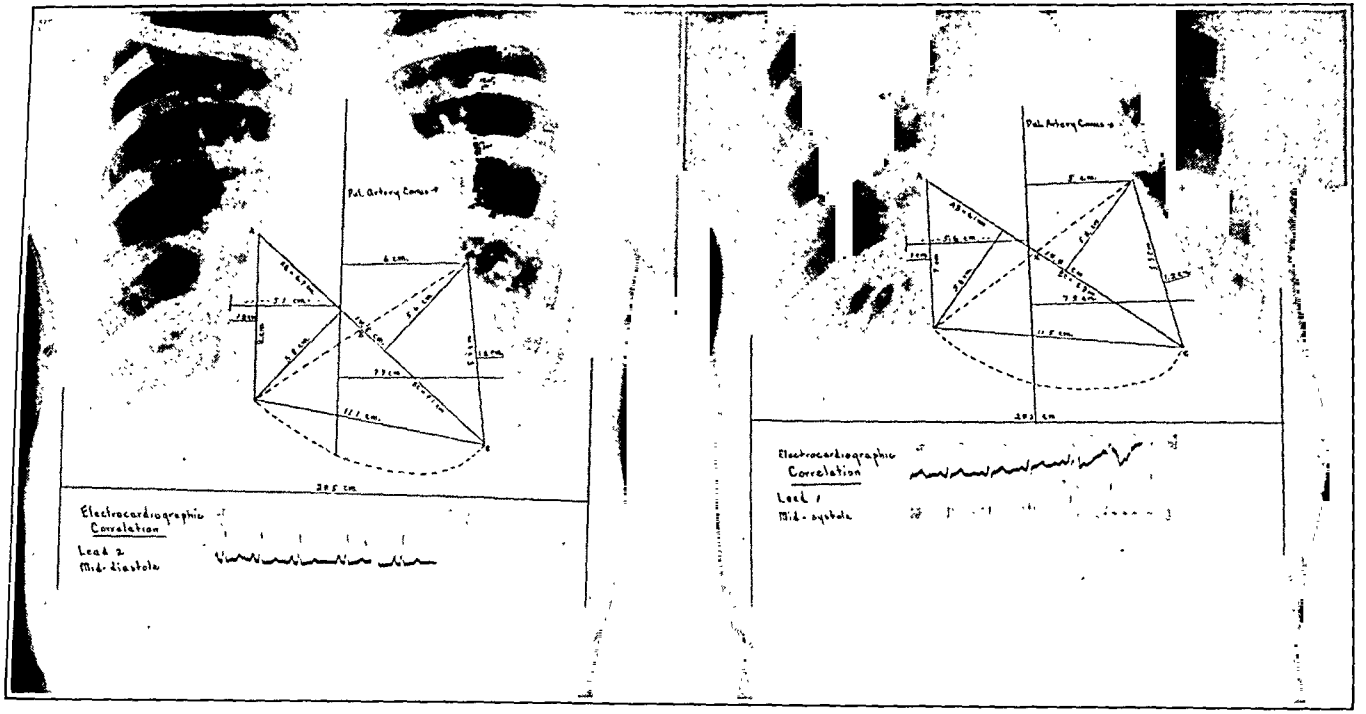


FIG. 1 FIG. 2

FIGS. 1 and 2.—Roentgenograms of the heart in diastole and systole.

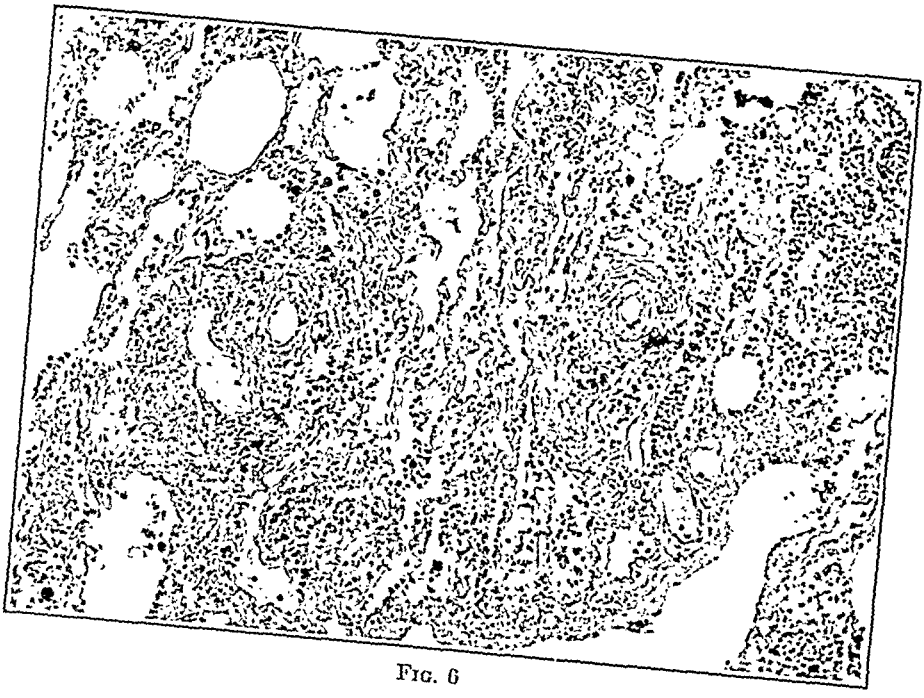


FIG. 6

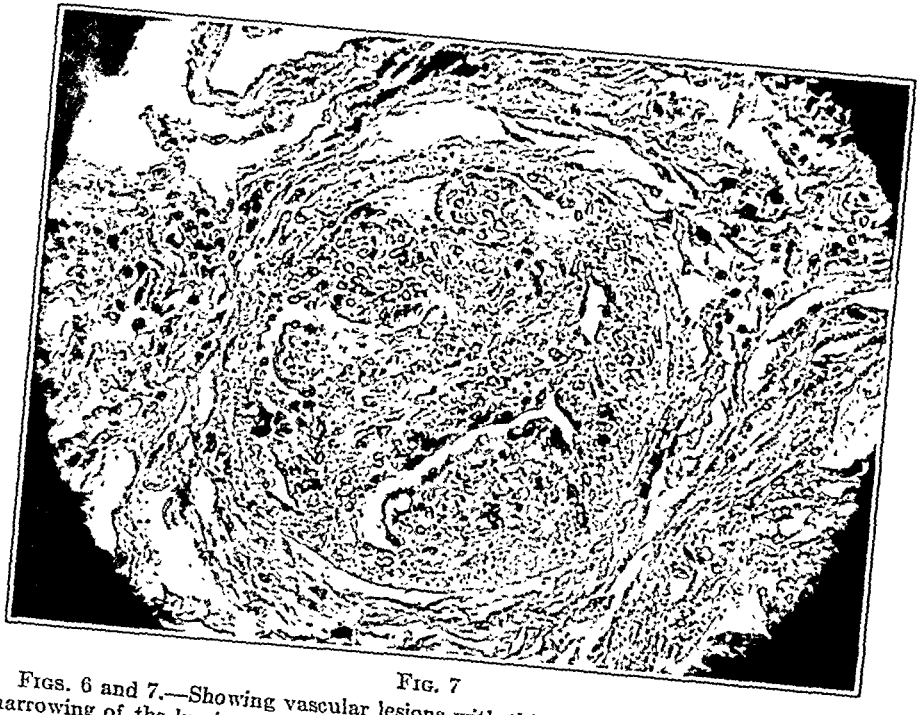


FIG. 7

FIGS. 6 and 7.—Showing vascular lesions with thickening of the vessel walls and narrowing of the lumina. Fig 7 shows an organizing thrombus within the vessel lumen.

TABLE 1.—SUMMARY OF HEMOCYTOLOGIC DATA AND FACTORS WHICH MIGHT BE EXPECTED TO INFLUENCE THE BLOOD PICTURE.

Date.	Hgb. gm. per 100 cc.	R. B. C., millions per c.mm.	Retic., %.	W. B. C., thousands per c.mm.	P. M. N., %.	P. M. E., %.	P. M. B., %.	Lymph., %.	Monoc., %.	Platelets thousands per c.mm.	Miscellaneous.
Dec. 12, 1932	17.6	7.48	...	9.1	73	2	..	22	3	...	Initial reading, Denver. 2 gm. phenylhydrazin Dec. 12, 1932 to Jan. 20, 1933.
Jan. 23, 1933	17.6	7.46	...	7.8	65	4	1	24	6	...	Hemorrhoidectomy. Anal hemorrhage for 1 week.
Jan. 31	15.0	5.65	...	10.6	81	2	..	17			Hemoglobin study.
Feb. 3	16.9	6.26	...		..	..	..	..	..	...	
Feb. 17	17.6	6.1	...	13.2	80	2	..	18	..	...	Acute respiratory infection.
Feb. 23	20.4	6.93	...	6.55	75	..	..	17	8	...	Blood volume study.
Mar. 28	17.6	7.17	...		..	..	..	..	..	...	From Denver to Columbus.
April 6	14.0	6.3	...	8.4	60	7	1	26	6	...	Initial reading, Columbus.
April 12	13.5	4.87	1.8	7.5	87	1	..	29	13		
April 18	16.0	4.9	0.6	4.9	54	11	1	22	12	210	
April 19	15.3	5.66	...	6.3	61	3	3	31	2	100	
April 20	14.0	5.75	0.2	5.05	56	1	1	28	14	80	
May 12	14.0	5.35	0.8	7.25	66	5	2	18	8	...	1 myelocyte.
June 9	15.3	6.12	3.4	6.8	78	4	..	12	6	...	Day of operation.

TABLE 2.—PERCENTAGES OF POSITIVE JUDGMENTS ON TASTE OF NaCl SOLUTIONS, WITH THRESHOLDS AT VARIOUS TEMPERATURES.

Dates in May.	10th.	12th.	5th.	8th.	16th.	17th.	11th.	4th.	19th.	22d.	23d.
Sol. temp., °C.	3	9	18	23	33	35	37	37	42	42	47
% NaCl											
.070		0		0							
.075			0	10							
.080		20	6	35	36						
.085			20								
.090	20	26	33		44					5	0
.095				55							
.100	35	55	53		84	0			48	40	10
.105				75							
.110	55	66.6	60		80	10			72	70	55
.115				94							
.120	55	86.6			76	15			75	80	80
.125				100							
.130	85	93.3			65	55			94	85	75
.135											
.140					70	65				100	70
.145											
.150						90	15	0			
.160						100	35	26.6			
.170							45	26.6			
.180							65	33.3			
.190							80	86.5			
.200							85	73.0			
.210							100				
Thresholds	.1075	.098	.098	.0925	.0915	.12875	.1725	.1832	.1008	.1033	.109

NOTE: Oral temperature was taken on each day and varied from 96.8 to 98.6° F.

When the patient took as much salt as she desired, it will be noted that the fluid intake and output averaged slightly higher than normal, that the urinary salt output although high was far below the salt intake and that

the whole blood and plasma chlorids were within normal limits. When salt was deleted from the diet the fluid intake and output became moderately diminished, the urinary salt output became less and both the whole blood and plasma chlorids showed a sharp and marked increase.

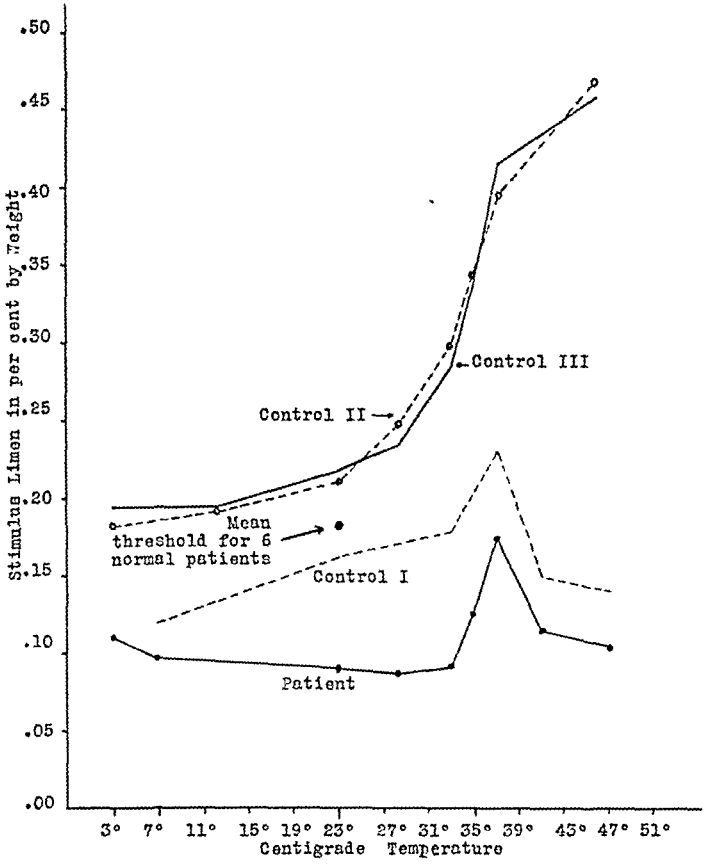


FIG. 3.—The influence of solution temperature on the stimulus limens for sodium chlorid.

TABLE 3.—CONSECUTIVE DAILY COMPARISONS OF FLUID INTAKE AND OUTPUT, SALT INTAKE, URINARY CHLORID AND BLOOD CHLORID.

Date.	Intake, water.	Total urine.	Intake, salt, gm.	Urinary chlorid, gm.	Urinary chlorid, %.	Blood chlorid, mg. per 100 cc. Whole blood.	Blood chlorid, mg. per 100 cc. Blood plasma.
April 21	2740	3200	90	22.88	0.71	495	559
April 22	2110	1250	30	21.93	1.73	478	577
April 23	2090	2000	135	22.6	1.13	478	643
April 24	2490	1900	30	11.21	0.59		
May 9	1885	1250	60	9.75	0.78	495	627
May 10	2160	1725	0	15.69	0.91	511	627
May 11	1400	900	0	11.7	1.30	578	643
May 12	1365	1100	...	11.4	1.04		
May 30	1350	1900	120			462	561
May 31	1400	2750	120	21.25	0.78	426	610
June 1	730	2300	60	14.94	0.65	500	618
June 2	1100	3750	60	34.12	0.91	462	610
June 3	1000	2600	0	20.28	0.78	432	594
June 4	700	2200	0	8.58	0.39	561	643
June 5	1080	500	0	2.60	0.52	561	660
June 6	1400	1250	...	6.5	0.52		

On June 10, at the request of the patient, an exploratory operation on the pulmonary artery was performed by Dr. G. Curtis. The pulmonary artery was large. The heart was found to have rotated to the right in a clockwise direction throwing the pulmonary artery to the right and the aorta to the left and anteriorly. No gross obstruction was found and closure was made. During convalescence the patient developed bronchopneumonia from which she died on June 12, 1933.

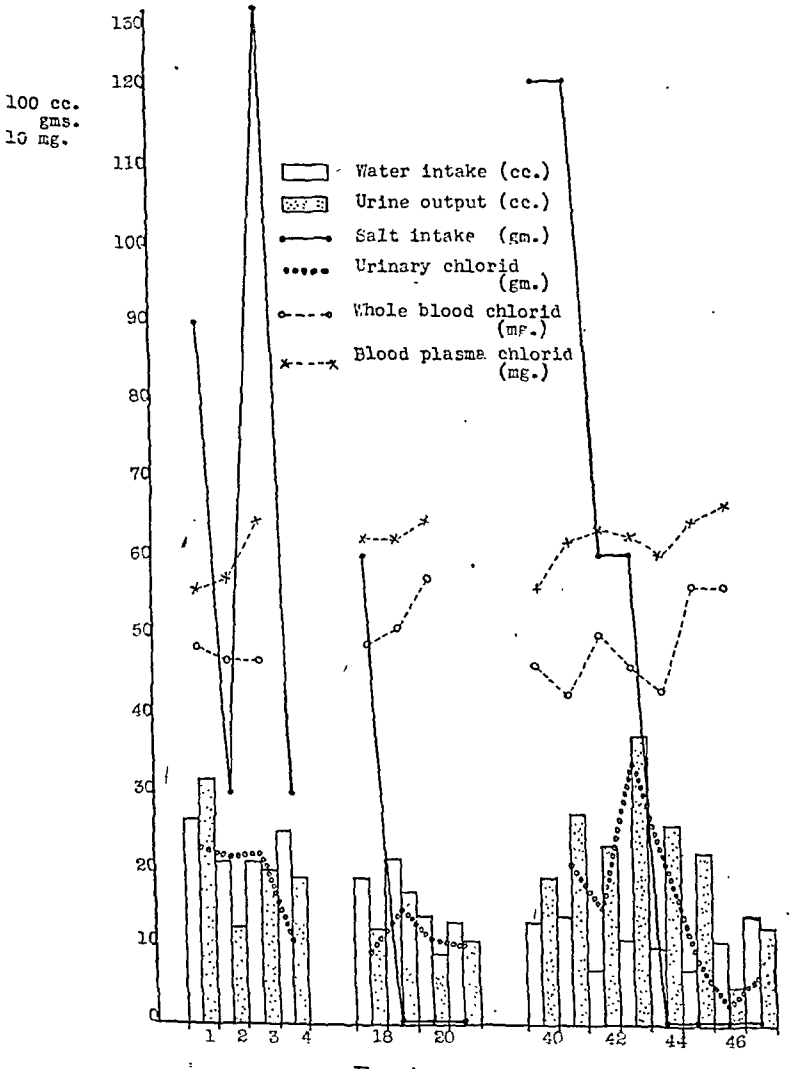


FIG. 4

Partial Autopsy (Dr. E. Scott). The heart weighed 330 gm. The right ventricle was prominent and on palpation was firmer than normal. The subpericardial fat and coronary arteries did not appear abnormal. The pulmonary artery was dilated, measuring 30 by 38 mm. and its walls were somewhat thickened. The aorta measured 22 by 24 mm. The tricuspid valve (10 cm. in circumference) showed slight diffuse thickening of the cusps but was competent. The pulmonary valves were normal (7 cm.); the mitral valve (7 cm.) was competent. The cusps were similar to those

of the tricuspid valve. The right ventricular wall measured 14 mm. in thickness; the left at the base of the papillary muscle, 12 mm. The aortic valves were normal (Fig. 5.)

MICROSCOPIC FINDINGS. *Aorta.* A moderate degree of atheromatosis was found in the subintimal coat, the media appeared normal save for very slight infiltration of the outer margin and the adventitial coat contained a few more lymphocytic and monocytic cells than might be termed entirely normal. The changes were not regarded as sufficient to warrant a diagnosis of luetic aortitis.

The pulmonary artery was slightly thickened and fibrotic. The median layer was normal. A slight cellular infiltration of the adventitia was noted similar to that found in the aorta.

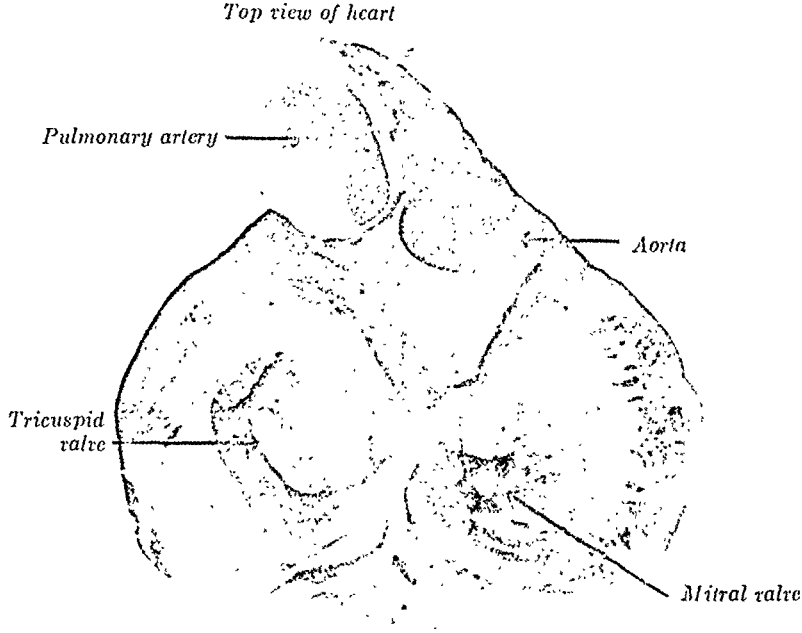


FIG. 5

Spleen. Moderate thickening of the capsule, some increase in stroma, rather diffuse increase in fibroblasts, a diminution in the pulp substance and some destruction of Malpighian corpuscles. The bloodvessels were generally thickened, chiefly due to adventitial fibrosis. In some of the smaller branches of the arterioles of the Malpighian bodies, there was some hyalin change involving the subintimal and median coats.

Liver. There was slight swelling of the liver cells. The interlobular branches of the hepatic artery were thickened due to adventitial fibrosis. The interlobular fibrous tissue in general was slightly increased.

Lungs. Microscopic changes characteristic of [illegible] were found. Sections from near the hili revealed [illegible] erosis and thickening of the branches of the pulmonary artery. The sclerosis was characterized by a thickening of the adventitial coat. These changes were conspicuous in both the large and median sized branches of the artery. In the smaller arterial divisions there was a proliferation on the part of the media which appeared to account entirely for the vessel thickening. In the precapillary vessels in many instances there appeared to be an endar-

teritis with almost complete occlusion of the vessel lumen. Occasionally changes which appeared to be those of thrombosis were found and in one vessel the resemblance to an organized thrombus with canalization was suggested (Figs. 6 and 7).

Discussion. In 1929, Moschcowitz's[3] excellent review of the causes and dynamics of pulmonary hypertension explained the clinical features in the light of physiologic compensation. Given the existence of hypertension in the lesser circulation, this author relates the sequence of events as follows: increased pulmonary diastolic pressure; overload to the right ventricle; right myocardial weakness with incomplete systolic discharge; overload to the right auricle; increased venous pressure with slowed capillary circulation. The anoxemia which results from incomplete oxygenation of the blood in the lungs and from increased deoxygenation of the blood in the tissues induces dyspnea, cyanosis and erythremia. The cyanosis is intensified by the polycythemia and by the venous stasis at the body surfaces. As the obstruction to the pulmonary circulation is prolonged and gradually increased in degree certain compensatory changes occur in the right heart (dilatation and hypertrophy) and in the pulmonary arteries (dilatation and sclerosis). The proliferative process in the pulmonary arteries adds in turn to the primary factors in the circulatory obstruction. As the result of this vicious cycle, tricuspid insufficiency must eventually develop with a still greater increase in venous pressure and in anoxemia. Venous stasis becomes more marked, swelling of the abdominal organs and ascites occur, dependent edema becomes pronounced and systemic diastolic pressure rises. The heart which is overburdened by increased venous return and increased peripheral resistance and which is undernourished because of decreased coronary flow and the marked anoxemia must eventually cease to function.

Clinically the course of pulmonary hypertension may be divided into two periods, the one before and the other after the onset of tricuspid incompetency. The first period may last for many years with the symptoms predominantly respiratory: in comparison the second period is much shorter with the symptoms predominantly cardiac.

Considered in the light of this general but brief discussion, our case fits into the picture as one presenting the clinical syndrome of obstruction to the lesser circulation prior to the onset of tricuspid incompetency. The clinical and laboratory findings important to the diagnosis, which for the most part have been previously reported in the literature, will be discussed but briefly save as they may show unusual deviation or seem to take on added significance.

The respiratory studies based upon the normals established by Dreyer and Hanson[4] revealed that the tidal air of our patient was greatly increased. We feel that this, as well as the dyspnea and

erythremia, represents an effort at compensation on the part of the respiratory mechanism and that such a finding is to be expected in the absence of accompanying pulmonary pathology.

That the increased red count noted in our patient represented a true erythremia was indicated by the increased whole blood volume. While an actual erythremia is usual in the syndrome of obstruction in the lesser circulation[5–9] the same observation has been made occasionally in patients living at high altitudes. In these cases, according to Monge,[10] the blood findings become normal on return to sea level. A normal individual with an adequate biologic mechanism of adaptation should show only temporary polycythemic changes on going to a high altitude. The fact that our patient's dyspnea became chronically aggravated in the Rocky Mountain region and the fact that her erythrocyte count and hemoglobin receded to normal shortly after her return to near sea level must indicate that her sojourn of more than a year in a mile-high altitude was a contributing cause of the erythremia. It seems reasonable that the lowered oxygen tension of high altitude would greatly aggravate the tendency toward polycythemia already present in an individual such as our patient with an obstruction in the pulmonary circulation.

It will be noted that the systolic and pulse pressures in our case were persistently low. It appeared to us that this might be of diagnostic significance in cases of obstruction to the lesser circulation for this reason: due to a narrowing of the pulmonary capillary bed the flow of blood to the left heart would be lessened which in turn would result in a low systolic and a small pulse pressure because of a lessened left ventricular discharge. Similar cases in which the blood pressures were reported[11–15] would seem to confirm our observation. Pund and Phinizy[16] particularly call attention to the low pulse pressure found in their case of pulmonary arteriosclerosis. It is also of significance that in the experimental work of Smith *et al.*,[17] which will be referred to later, it was noted that the systolic pressures became much lower in the animals which developed pulmonary arteriosclerosis.

The experimental work on the taste sensitivity of this patient for sodium chlorid is of considerable interest. Her salt intake was several hundred times that of each of 6 normal subjects. When the average taste threshold for sodium chlorid of these 6 persons was contrasted with that of our patient, it was found that her threshold was surprisingly low (0.185 as compared with 0.092). It would seem to us that an individual regularly taking such large quantities of salt would more logically be expected to manifest a decrease in taste sensitivity rather than an increase.

Whether or not the high salt intake noted represents a perversion of appetite or a metabolic or endocrine disturbance cannot be judged. Human cases of osmotic poisoning and even death from

the ingestion of sodium chlorid have been recorded. The literature contains many experimental studies involving a high sodium chlorid intake for relatively short periods of time but the prolongation of high salt intake noted in this patient is, so far as we have been able to determine, without parallel in the medical literature except for the reports of Thompson and McQuarrie[18] and McQuarrie.[19] These observers mention 4 cases of juvenile diabetes mellitus in which an abnormal craving for and ingestion of large quantities of sodium chlorid (as high as 80 gm. daily) was present. These patients presented a peripheral hypertension and a high fluid intake and output, all of which disappeared on removing the excess salt from the diet. When we compare the findings in our case we note, first, that our patient did not have diabetes; second, that she presented a peripheral hypotension; third, that her fluid intake and output did not closely parallel her salt intake; and fourth, that she appeared to be unable to delete the large amount of salt from her diet.

While the observations noted are of diagnostic and clinical interest, they contribute nothing toward an understanding of the etiology in this case. Moschcowitz[3] emphasizes that pulmonary arteriosclerosis (save the atheromatosis found in the aged) always indicates that hypertension of the lesser circulation is or has been present. With probably few exceptions (congenital heart disease with arteriovenous shunt and primary pulmonary hypertension) such hypertension is secondary to obstruction in the pulmonary circuit, which, if sufficiently prolonged, results in sclerosis of the arteries. From the following discussion it will be apparent that no definite cause of hypertension, other than the arterial and arteriolar hyperplasia, is evident. Many possible causes, however, present themselves and we have chosen to discuss these possibilities in 3 groups: the first considers congenital abnormalities of the heart and pulmonary vessels; the second, extravascular conditions of the lungs; the third, primary defects occurring in the pulmonary arteries and arterioles themselves.

If the statement that cyanosis appeared at 3 weeks of age is to be depended upon, it is probable that this individual was born with an inadequate circulo-respiratory mechanism. At autopsy no congenital cardiac defects were found. It is conceivable that malposition of the heart such as was found in our case might have resulted in constriction of any of the great vessels of the hilar regions but no evidence of such constriction was found. The dilatation of the pulmonary artery and the sclerosis of the smaller arteries throughout both lungs indicate obstruction acting in or on the arterioles and capillary bed or the venous system. A congenital hyperplasia of the arteries and arterioles could fit into such a picture and has been considered as an etiologic possibility by Steinberg[20] and Sisto.[21] That congenital sclerosis of arteries may occur has

been shown by the observations of Kissane and Fidler.[22] These authors report 1 case of congenital sclerosis of the coronary arteries and they review many similar cases from the literature, many of which were apparently secondary to intrauterine fetal infections. Narrowing of the pulmonary veins in pulmonary arteriosclerosis has been observed (Wätjen[23]) but according to Ljungdall[24] this should be considered as secondary to the diminished inflow of blood and not as a cause of increased resistance. Consequently such cases would involve a primary congenital hyperplasia of the arteries and arterioles.

Aside from cyanosis, definite symptoms suggesting a cardio-respiratory condition did not manifest themselves until our patient was 4 years old. This suggests that events occurring or developing prior to the age of 4 might have served to accentuate a congenital cardio-respiratory condition or that the early observation of cyanosis was incorrect in which case such events might primarily account for the condition. The first of several attacks of pneumonia and the onset of an abnormal appetite for salt occurred before our patient reached the age of 4 years and should perhaps be considered in this regard.

The repeated attacks of pneumonia during early childhood may well have been associated with a chronic interstitial pneumonitis and have resulted in hypertension for a sufficient period to initiate arteriosclerotic changes. With the ultimate resolution of the infection, pulmonary arteriosclerosis and hypertension would have remained.

Since a prolonged high salt intake had been so prominent in our case, the possibility that this might result in pulmonary arteriosclerosis must be thought of. It has recently been shown (Smith *et al.*[17]) that in rats chronic pulmonary edema induced by the prolonged inhalation of oxygen can cause alveolar fibrosis and pulmonary arteriosclerosis. With continued exposure to oxygen the edema disappears but the arteriosclerosis and alveolar changes persist. Listing the experimental methods of inducing pulmonary edema, Wiggers[25] mentions the intravenous injection of saline solutions. One of us (W. D.) was able to induce fatal pulmonary edema in rabbits following the oral administration of large daily doses of salt over a period of from 1 to 6 weeks. No evidence, however, of pulmonary or peripheral arteriosclerosis could be found in these animals postmortem. A small series of young mice was likewise maintained upon a standard diet containing from 3 to 5% salt for as long as 6 months; microscopic examination of the lungs and other tissues revealed no evidence of arteriosclerosis. It has previously been noted that peripheral hypertension was present in the cases of high salt intake reported by Thompson and McQuarrie.[18,19] These observers also noted an elevation of the peripheral blood pressure in normal individuals who ingested a comparative

dosage of salt. Such investigations and observations, while not extensive, would seem to indicate the unlikelihood that a prolonged high salt intake could induce an independent hypertension in the lesser circulation.

Although the above etiologic possibilities may apply to certain cases, it is apparent that in our case the cause cannot be proven to be due to a congenital cardiac or vascular abnormality or to an extravascular pulmonary condition. Consequently the probability of a cause arising or existing primarily in the pulmonary arteries and arterioles themselves must be considered. But few carefully studied cases of primary pulmonary arteriosclerosis have been reported. Hare and Ross,[11] after a careful review of the literature before 1929, felt that only 23 cases justified such a designation. They added one more of their own. Excellent papers upon the subject have also been published by Steinberg,[20] Sisto,[21] Pund and Phinizy[16] and Ulrich.[26] It thus becomes evident that in the cases of primary pulmonary arteriosclerosis certain characteristics are apt to appear which are infrequent or absent in the secondary cases. The secondary sclerosis is most apt to occur (save in patients with congenital heart disease) after 40, while the primary condition is more prone to develop in younger individuals. Clubbing of the fingers is less likely to be present in the primary than in the secondary cases. If the condition is primary, the sclerosis is more or less confined to the small arteries and arterioles and the hypertrophy of the right heart is most marked. If the condition is secondary, the sclerosis is more apt to involve the large arteries and the hypertrophy of the right heart is less conspicuous. It is evident that in all these respects our case appears to be one of primary pulmonary arteriosclerosis.

Syphilis (as proven by characteristic histopathologic findings) is undoubtedly the most frequent cause of primary pulmonary arteriosclerosis. Our case showed no characteristic findings of syphilitic arteritis in sections of the lung, which, according to present standards, is sufficient to rule out such a diagnosis.

Sokoloff and Stewart[27] have reported a case in which, although a history of severe asthmatic paroxysms requiring frequent and large doses of adrenalin was present, an endocrine cause was considered. Unfortunately permission for an abdominal and cranial autopsy was refused by the relatives of our patient and no data regarding the adrenals or pituitary is available. It is possible that the high salt intake noted in our patient may have been a manifestation of some unusual malfunction of the adrenal or pituitary glands. There is this possibility but no clinical evidence of endocrinopathy was demonstrable.

Instances of apparent idiopathic pulmonary arteriosclerosis have been reported. Hare and Ross,[11] in 1929, gathered 7 such cases from the literature. One more has since been reported by Pund

and Phinizy[16] and 2 by Ulrich.[26] Two of the cases found in the literature by Hare and Ross and the case of Pund and Phinizy were luetics, but microscopic examination of the pulmonary vessels ruled out a syphilitic arteritis. Consequently these 3 cases may be included in the idiopathic group. It is interesting that these cases of unknown etiology are found in young adults; the average age of the above cases being 29 years and, if those with lues are excluded, 23.2 years. If age is significant, our patient would seem to fit in with this small group of idiopathic cases and we feel that, while several etiologic bases for the condition found in our patient have been presented for consideration, the proof for the underlying cause remains incomplete. Therefore, we prefer to classify our case as one of primary pulmonary arteriosclerosis of unknown etiology—at least until it can again be reviewed in the light of greater knowledge than we now possess.

Summary. The case herewith presented is that of a young female, aged 20, who since early childhood had manifested the signs and symptoms of obstruction in the lesser circulation. Autopsy revealed marked pulmonary arteriolar sclerosis, dilatation of the pulmonary artery and right ventricular hypertrophy.

During most of her life the patient had ingested abnormally large amounts of salt (as much as 3 pounds in 1 week). No cause for this abnormality could be found. It is of interest that her taste threshold for salt was much lower than the thresholds of persons who were normal in respect to salt desire and intake, that her fluid intake and output were not materially disturbed by variations in salt intake and that the osmotic pressure and the chemistry of the blood were not altered.

The case is discussed at length from the standpoint of possible causes of arteriosclerosis. Moschcowitz insists that, save with very few exceptions, pulmonary arteriosclerosis is the result of long-standing hypertension in the lesser circulation. Most such cases of hypertension are secondary to congenital abnormalities of the heart or pulmonary vessels or to extravascular or intravascular circulatory obstruction. In this patient we were unable to demonstrate any cause of obstruction or hypertension in the lesser circulation other than the arteriolar hyperplasia itself. Consequently we consider this case to be one of primary pulmonary arteriosclerosis and, since microscopic examination of the pulmonary tissue failed to reveal any evidence of luetic arteritis, we feel that it should be further classified as one of unknown etiology.

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VARIATIONS IN SYSTOLIC BLOOD PRESSURE IN RENAL TUMOR: A STUDY OF 491 CASES.

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The kidney has always played a major rôle in any discussion of the cause of hypertension. There is justification for this because, in the majority of subjects with hypertension, the renal parenchyma is profoundly altered. Despite this fact and the volume of work which has been done to establish the cause of this alteration, an adequate explanation has not yet been found. Renal tumors have at various times been mentioned as a basis for hypertension,[10,11] and indeed an increased arterial tension has been cited as evidence valuable for clinical identification of a renal tumor.[3]

The commonest tumor of the kidney, the so-called hypernephroma, derives its name from the close histologic relationship it bears to the suprarenal cortex. Hypertension was noted by some observers

in persons who had hypernephroma, and because of the resemblance of the tumor to suprarenal tissue it was postulated that the hypertension was caused by an excessive production by the tissue of the tumor of a pressor substance analogous to that produced by the normal suprarenal gland. There are numerous reports[5,8,9] of marked clinical hypertension among patients who were later shown to have suprarenal tumors, and in some cases relief of the hypertension was afforded by removal of the tumor. Not all these tumors were of like histologic structure. Some appeared to be derived from the cortical tissue and others from the medullary tissue of the suprarenal gland.

Various types of tumors have been observed in cases of paroxysmal hypertension. C. H. Mayo[7] reported one of the first verified cases. On exploration he found an oval retroperitoneal mass, 6 by 4 cm., situated behind the tail of the pancreas on the mesial side of the left kidney and impinging against the upper pole. The tumor was removed. It appeared to be composed of nerve tissue containing ganglion-like cells, but because of the absence of marked differentiation this analogy was in no way complete. After fixation in formaldehyde the grayish color of the tumor changed to an orange-yellow, giving the mass the appearance of a suprarenal cortical adenoma, but the characteristic differentiated cells in glandular arrangement were lacking. A diagnosis was made of a malignant retroperitoneal blastoma. The attacks of paroxysmal hypertension ceased after removal of the tumor. Since this time reports of 8 similar cases, the tumors being identified at surgical exploration, have appeared in the literature.

Although authentic instances are few in number, it is nevertheless generally considered that a hypernephroma of renal origin usually causes an elevation in the blood pressure. Volhard observed 2 cases of hypernephroma in which occurred the diffuse clinical picture of hypertensive nephritis with albuminuria and a rise in blood pressure, both phenomena disappearing as soon as the tumor was removed. Voelcker and Boeminghaus stated that a sharp rise in blood pressure was noticed by many observers among patients suffering from renal tumors, and that since this phenomenon is connected with an increased production of epinephrin in Grawitz tumors (hypernephromas), so an extraordinarily high blood pressure supervening in the case of a pre-existing renal tumor can give an indication of the histopathologic nature of the tumor. Ljunggren[6] cited Voelcker's views and analogous ones of Blum but was unable to find epinephrin in the renal tumors which he analyzed. In 12 cases of hypernephroma in which adequate studies of blood pressure had been made he found no decrease in the arterial tension after surgical removal of the tumor. He therefore concluded that hypernephromas do not obviously produce a substance which increases the blood pressure.

Federoff used Ehrmann's enucleated frog's-eye test for epinephrin to demonstrate an excess of an epinephrin-like substance in a hypernephroma. He was unable to find a similar substance in control renal tissue and cited this as an aid in establishing the diagnosis of hypernephroma. Greer and Wells,[4] in 1909, and Brooks,[1] in 1911, were unsuccessful in attempts to confirm Federoff's work. These workers searched for an epinephrin-like substance, by the intravenous injection of tissue extract into dogs, and watched for a rise in blood pressure by Ehrmann's[2] enucleated frog's eye test and by colorimetric means. Brooks found no epinephrin-like substance in specimens of blood from 3 patients suffering respectively from a malignant hypernephroma, metastatic lesions from a hypernephroma-like suprarenal tumor, and 2 typical renal hypernephromas. This is as one would expect because a hypernephroma resembles suprarenal cortex, which portion of the suprarenal gland plays no part in the production of epinephrin.

It was in the hope that aid in clarifying this situation would be obtained by an adequate analysis of the blood pressures of persons suffering from renal tumors that the present study was undertaken, particularly since it seemed to us that heretofore any statements of the relation of renal tumors to systolic blood pressure were made on a conviction reached by a study of isolated cases.

The material used for study consisted of the records of patients with renal tumors who were admitted to the clinic between 1912 and 1934. We considered a total of 491 cases of all types, in which 340 (69%), of the patients were males and 151 (31%) females. In 459 cases there was a record of the pre-operative systolic blood pressure. Since the only readings of blood pressure noted were often those taken when the patient was first seen at the clinic, for the sake of uniformity we have used only these primary readings. Though the readings were taken by different persons, and though estimations of blood pressure taken with the patient under the considerable nervous strain of the first visit are admittedly higher than those which must be considered normal for each patient, we feel that the error so introduced will be negligible and is certainly unavoidable when records over such a long period must be relied on.

We have arbitrarily divided our renal tumors into two groups: (1) hypernephromas, and (2) tumors of other types, which included papillary squamous-cell epitheliomas, sarcomas, hemangio-endotheliomas, and so forth. In 335 cases in which the blood pressure was recorded pre-operatively, a pathologic diagnosis of renal adenocarcinoma of the hypernephroma type was made, 247 of the patients being males, 88 females.

Considering the males with hypernephroma (Table 1), we noted that they range in age from 10 to 80 years, the majority (72%) being between 45 and 65. Of this group 60% had a blood pressure between 100 and 139 mm. of mercury (which we are considering as a normal

range for our present study), 0.8% had definite hypotension, that is, a systolic pressure less than 100, and 39.2% had hypertension, that is, a systolic pressure of 140 or more. When we plotted the actual readings of blood pressure and superimposed the arithmetic mean of the different age groups in the form of a curve (Fig. 1) we found that this closely approached the curve obtained by plotting the arithmetic mean for the different age groups obtained by a similar analysis of a large series of normal males, being perhaps slightly, but hardly significantly elevated above the normal value.

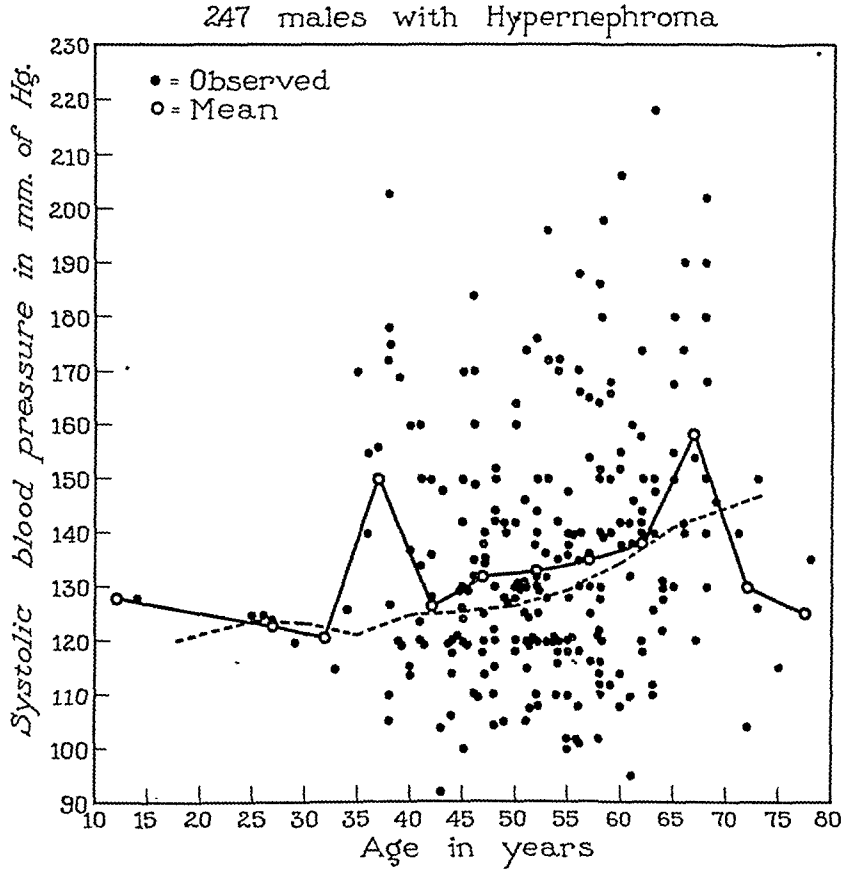


FIG. 1.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal males.

The postoperative blood pressure was recorded for 81 of the males who had hypernephroma (Table 2). The interval elapsing between operation and the time the postoperative reading was obtained varied from a few days to several years in some instances. Of these 81 males, 63.1% had a systolic pressure between 100 and 139, 1.2% had a systolic pressure less than 100, and 34.7% had a reading of 140 or more. These incidences are almost identical with those in similar

groups prior to removal of the tumor. When these readings were plotted (Fig. 2) and the arithmetic means superimposed in the form of a curve, the mean values were again found very closely to approximate the mean for normal males. In short, our observations derived from an analysis of the pre-operative and postoperative records of the blood pressure of males with hypernephroma would lead us to suspect that a hypernephroma does not cause a consistent elevation

TABLE 1.—SYSTOLIC BLOOD PRESSURES OF 247 MALES WITH HYPERNEPHROMA.

Systolic blood pressure in mm. of mercury.	Age, years.													Total.	Per cent.	
	10 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70 to 74	75 to 79		
90 to 99	...	...	...	...	...	...	1	...	...	...	1	...	...	...	2	0.8
100 to 109	...	...	...	...	...	1	2	3	3	6	1	...	1	...	17	6.9
110 to 119	...	...	...	...	1	1	4	6	6	9	6	...	1	1	35	14.2
120 to 129	1	...	...	4	1	3	8	10	14	8	4	1	1	...	55	22.3
130 to 139	...	...	...	...	...	1	3	9	12	7	5	2	1	1	41	16.6
140 to 149	...	...	...	...	...	2	1	7	5	7	9	4	1	...	36	14.6
150 to 159	...	...	...	...	...	1	2	3	2	4	5	4	...	...	21	8.5
160 to 169	...	...	...	...	...	4	2	1	2	5	1	2	...	...	17	6.8
170 to 179	...	...	...	...	...	...	...	2	5	1	1	1	...	...	10	4.1
180 to 189	...	...	...	...	...	...	...	1	...	3	...	2	...	...	6	2.4
190 to 199	...	...	...	...	...	...	...	...	...	1	...	2	...	...	3	1.2
200 to 209	...	...	...	...	...	1	...	...	...	...	1	1	...	...	3	1.2
210 to 219	...	...	...	...	...	...	...	...	...	...	1	...	...	...	1	0.4
Average pressure	128	...	...	124	121	150	127	132	133	135	139	158	130	125	136	
Total patients	1	...	...	4	2	14	23	42	49	51	35	19	5	2	247	

TABLE 2.—SYSTOLIC BLOOD PRESSURES OF 81 MALES AFTER NEPHRECTOMY FOR HYPERNEPHROMA.

Systolic blood pressure in mm. of mercury.	Age, years.									Total.	Per cent.
	25 to 29	30 to 34	35 to 39.	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69		
90 to 99	...	...	...	1	...	...	...	...	...	1	1.2
100 to 109	...	1	1	1	1	1	2	...	...	7	8.7
110 to 119	2	...	...	3	3	2	5	3	...	18	22.2
120 to 129	...	...	1	3	3	5	3	2	1	18	22.2
130 to 139	...	...	...	...	3	3	1	1	...	8	10.0
140 to 149	...	...	...	1	3	2	1	2	1	10	12.3
150 to 159	...	...	...	...	...	1	2	...	2	5	6.2
160 to 169	...	...	...	...	1	...	...	2	...	3	3.7
170 to 179	...	...	1	...	3	1	...	...	2	7	8.7
180 to 189	...	...	...	...	...	...	1	...	...	1	1.2
190 to 199	...	...	...	...	...	...	1	...	...	1	1.2
200 to 209											
210 to 219	...	...	...	...	...	1	...	1	...	2	2.4
Average pressure	111	106	130	115	135	135	131	140	151	133	
Total patients	2	1	3	9	17	16	16	11	6	81	

of blood pressure, and we did not verify Volhard's observation that a fall in arterial tension consistently followed surgical removal of a renal hypernephroma.

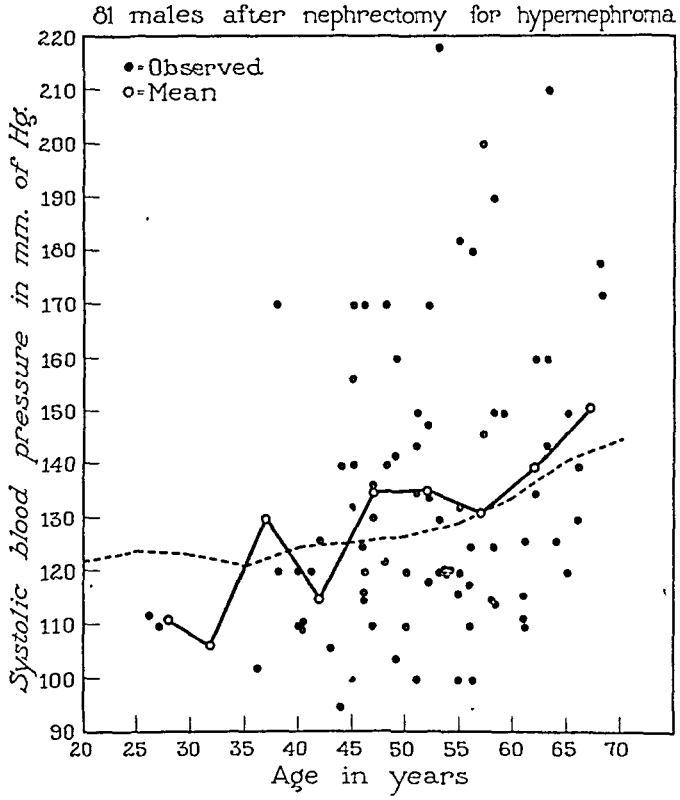


FIG. 2.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal males.

There were 88 females with hypernephromas for whom there was an available pre-operative record of the blood pressure (Table 3). Sixty-two (70.4%) ranged in age from 45 to 65. Of the eighty-eight, 45.3% had a systolic blood pressure between 100 and 139, 1.2% had a systolic blood pressure less than 100 and 53.5% had a reading of 140 or more. We plotted each reading and superimposed a curve representing the arithmetic mean for the various age groups (Fig. 3). Here again the mean value is found to approximate closely that obtained by a similar analysis of normal females, although it is consistently slightly higher. The postoperative blood pressure was recorded in 17 of these cases. Eight of the patients (47%) had a postoperative reading between 100 and 139, and 53% had a reading of 140 or more. That the incidence for the different ranges of blood pressure was practically unaltered by removal of the tumor seems to us to be significant.

TABLE 3.—SYSTOLIC BLOOD PRESSURES OF 88 FEMALES WITH HYPERNEPHROMA.

Systolic blood pressure in mm. of mercury.	Age, years.														Total.	Per cent.
	10 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70 to 74	75 to 79		
90 to 99	...	...	...	...	...	...	...	...	1	...	...	...	...	...	1	1.2
100 to 109	...	...	...	...	...	...	1	...	...	...	1	...	...	...	2	2.2
110 to 119	...	...	...	...	...	2	...	...	2	4	2	1	...	...	11	12.5
120 to 129	...	...	...	...	...	1	3	2	2	4	1	...	...	...	13	14.7
130 to 139	...	...	...	1	2	1	1	3	2	1	1	1	1	...	14	15.9
140 to 149	...	...	...	...	1	...	1	1	6	1	2	1	1	...	14	15.9
150 to 159	...	...	...	...	...	...	1	1	5	2	...	1	...	...	10	11.3
160 to 169	...	...	1	...	...	...	...	...	1	3	...	1	...	...	6	6.8
170 to 179	...	...	...	...	...	1	...	...	1	4	1	1	...	...	8	9.1
180 to 189	...	...	...	...	...	...	...	...	...	...	3	...	...	...	3	3.4
190 to 199	...	...	...	...	...	...	...	...	...	1	...	...	...	...	1	1.2
200 to 209	...	...	...	...	...	...	...	...	...	1	...	...	...	...	1	1.2
210 to 219	...	...	...	...	...	...	...	...	...	...	1	...	...	...	1	1.2
220 to 229	...	...	...	...	...	...	...	...	1	1	...	...	...	...	2	2.2
230 to 239	...	...	...	...	...	...	1	...	...	...	...	...	...	...	1	1.2
Average pressure	...	...	165	130	136	130	143	133	143	151	150	146	138	...	145	
Total patients	...	...	1	1	3	5	8	7	21	22	12	6	2	...	88	

TABLE 4.—SYSTOLIC BLOOD PRESSURES OF 76 MALES WITH RENAL TUMORS OTHER THAN HYPERNEPHROMA.

Systolic blood pressure in mm. of mercury.	Age, years.										Total.	Per cent.
	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70 to 74		
100 to 109	...	...	...	1	3	4	...	...	2	...	10	13.1
110 to 119	...	...	1	1	4	4	...	1	1	...	12	15.8
120 to 129	1	...	...	1	4	2	...	2	1	...	11	14.5
130 to 139	1	...	...	2	2	2	...	1	4	...	12	15.8
140 to 149	...	...	...	2	3	...	5	1	3	...	14	18.4
150 to 159	...	1	...	1	...	3	...	3	...	...	8	10.6
160 to 169	...	...	1	...	...	...	1	3	1	1	7	9.2
170 to 179												
180 to 189	...	...	...	...	...	...	1	...	...	...	1	1.3
190 to 199	...	...	...	...	...	...	...	1	...	...	1	1.3
Average pressure	125	150	140	129	122	122	150	147	132	160	132	
Total patients	2	1	2	8	16	15	7	12	12	1	76	

The mean pre-operative systolic blood pressure for the males with hypernephroma was 136, for the females 145. Though these values are admittedly elevated over those considered normal, if we are to consider that this is due to the pressor action of a substance secreted by the hypernephroma, we have no explanation why removal of the tumor does not consistently result in a lowering of the blood

pressure. That such a drop does not occur is evident from our analysis, and it is verified when we find that the mean postoperative value for the blood pressure of males and females who had hypernephroma is 133 and 144, respectively.

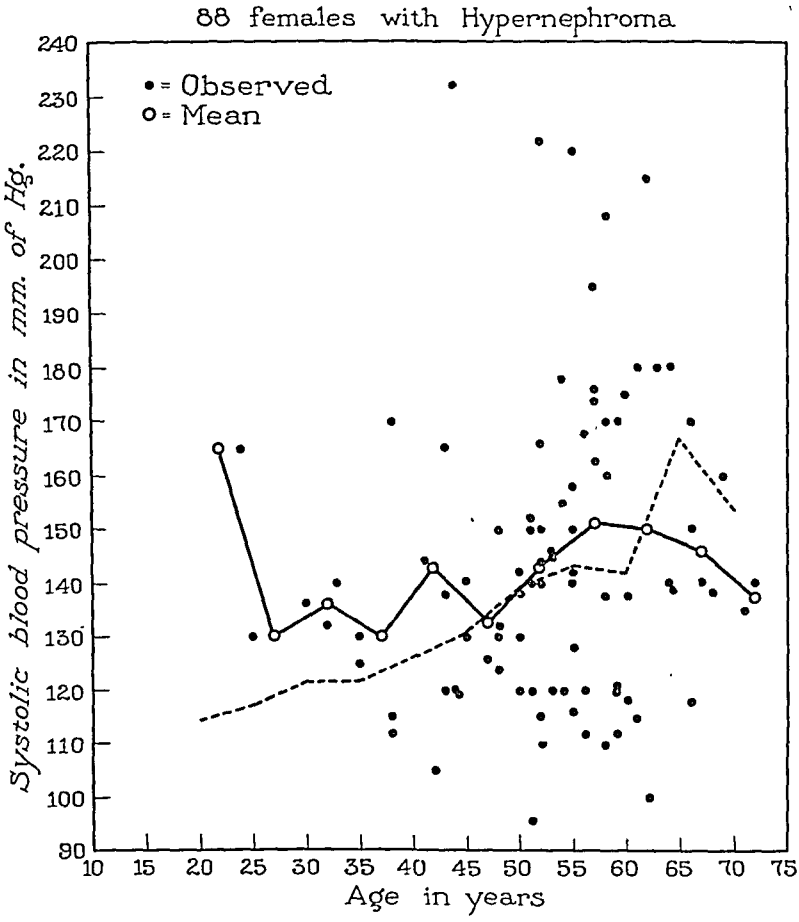


FIG. 3.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal females.

There were 76 males with renal tumors other than hypernephromas (Table 4), 59.2% having a systolic blood pressure between 100 and 139, and 40.8% a systolic blood pressure of 140 or more. This incidence is almost identical to that for like ranges of blood pressure among males with hypernephroma. The arithmetic mean for this group closely approximated the normal (Fig. 4). A postoperative record of the blood pressure was obtained in 24 cases; 66.7% had a reading between 100 and 139, 8.3% a reading less than 100, and 25% a reading of 140 or more.

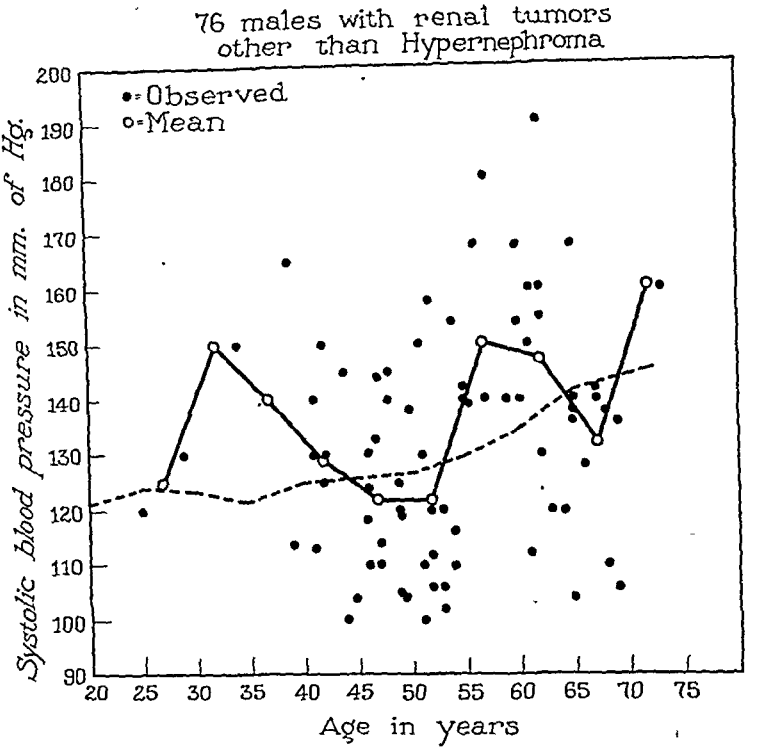


FIG. 4.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal males.

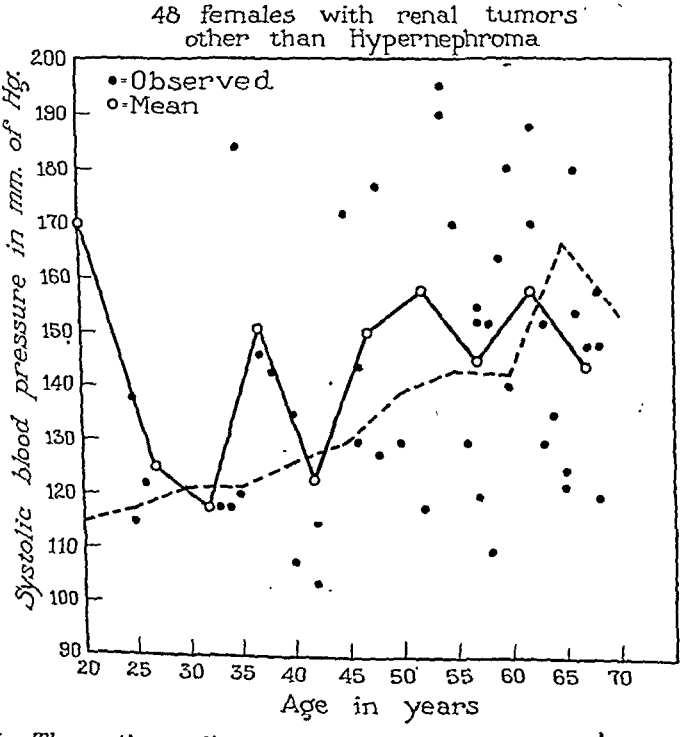


FIG. 5.—The continuous line is the curve of the mean systolic blood pressures. The broken line is a control curve representing the mean systolic blood pressures of normal females.

There were 48 females with renal tumors other than hypernephromas (Table 5), 45.8% of these having a systolic blood pressure between 100 and 139, and 54.2% one of 140 or more. It is to be noted that this percentage distribution is practically identical with that for the group of females with hypernephromas, and the arithmetic mean blood pressure closely approaches the normal value (Fig. 5). In 20 cases in which a postoperative record was made, 40% of the patients had a blood pressure between 100 and 139, 60% one of 140 or more.

TABLE 5.—SYSTOLIC BLOOD PRESSURES OF 48 FEMALES WITH RENAL TUMORS OTHER THAN HYPERNEPHROMA.

Systolic blood pressure in mm. of mercury.	Age, years											Total.	Per cent.
	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69		
100 to 109	...	...	...	...	...	2	...	...	...	...	...	2	4.1
110 to 119	...	...	1	2	...	1	...	1	1	...	...	6	12.5
120 to 129	...	...	1	...	1	...	1	...	1	...	3	7	14.6
130 to 139	...	...	1	...	...	1	1	1	1	2	...	7	14.6
140 to 149	...	...	...	...	2	...	1	...	...	...	2	5	10.5
150 to 159	...	...	...	...	...	1	...	...	3	2	2	8	16.7
160 to 169	1	...	...	...	1	...	...	...	1	...	...	3	6.3
170 to 179	...	...	...	...	...	...	2	...	1	1	...	4	8.3
180 to 189	...	...	...	...	1	...	...	...	...	2	1	4	8.3
190 to 199	...	...	...	...	...	...	...	2	...	...	...	2	4.1
Average pressure	169	..	125	118	151	123	150	158	145	158	144	145	
Total patients	1	...	3	2	5	5	5	4	8	7	8	48	

In our series there were 6 cases of hypernephroma in which a definite involvement of the suprarenal glands was proved, and of these a marked hypertension was present in only 2 cases. In 3 of these 6 cases the tumor seemed to arise primarily in the suprarenal gland. One of the patients had practically a normal blood pressure with a reading of 142 systolic and 84 diastolic. One had hypertension of moderate degree with a blood pressure of 190 systolic and 100 diastolic. The third patient had marked hypertension, with retinal arteriosclerosis, retinal hemorrhage, cardiac enlargement, and a blood pressure of 232 systolic and 145 diastolic. There was no postoperative record in any of these 3 cases. There were 19 cases in which definite suprarenal involvement was not proved histologically, but it should be inferred because of the origin of the tumor in the upper pole of the kidney and its extension to involve the diaphragm. In this group of cases hypertension existed in 4 cases; an absolute hypotension with a systolic reading of 96 was present in 1 case and there was a normal blood pressure in the others.

A summary of the findings reported is given in Table 6. This includes all patients with renal tumors, both males and females, records of whose blood pressures were available.

TABLE 6.—SUMMARY OF FINDINGS.

Before operation.	After operation.
Patients with Hypernephroma: 335	
188 had normal blood pressure.	42 still had normal blood pressure. 10 had hypertension.
	52*
144 had hypertension.	18 had normal blood pressure. 28 still had hypertension.
	46*
3 had hypotension.	No record.
Patients with other Renal Tumors: 124	
67 had normal blood pressure.	12 had normal blood pressure. 4 had hypertension. 2 had hypotension.
	18*
57 had hypertension.	11 had normal blood pressure. 14 still had hypertension.
	25*

* These figures represent total number of patients in the group whose blood pressure was recorded postoperatively. Records for the remainder were not available.

Comment. This analysis shows striking uniformity of the readings of systolic blood pressure for the various histologic types of renal tumor. Practically identical incidences for the different groups of blood pressure occurred both in cases of hypernephroma and in those of renal tumors of other types. No consistent alteration in blood pressure occurred following removal of a tumor of either type. This was particularly significant in cases of hypernephroma in which for both males and females as high an incidence of hypertension occurred after removal of the tumor as existed prior to operation. Scrutiny of the males with renal tumors other than hypernephroma would lead one to think that they experienced a diminution of arterial tension following operation, but since an exactly opposite situation existed with respect to the females, we can hardly attach significance to this. In conclusion, we found no constant increase in the blood pressure of patients who were suffering from renal tumors. In particular we failed to substantiate the observation of previous investigators: that a marked fall of an antecedent hypertension followed removal of a hypernephroma.

Finally, we would suggest that this study offers clinical evidence that an epinephrin-like pressor substance is not produced by the hypernephromatous type of renal tumor.

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THE DOSE OF ANTIBODY EFFECTIVE IN THE TREATMENT OF PNEUMOCOCCUS TYPE II PNEUMONIA.*

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In the specific serum therapy of pneumococcus Type II pneumonia, the importance of considering the amount of serum and the time at which it is given has been recognized by a number of physicians.[1–6] The experience at the Boston City Hospital during the last 6 years has brought out the significance of these factors. It is

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possible, on the basis of this experience, to offer a rational schedule of dosage for serum therapy and also to indicate some of its limitations.

The matter presented itself when we were confronted with two consecutive periods, of 3 years each, during which very divergent clinical results were obtained. During the period from November, 1929, through May, 1932, it was possible to demonstrate a considerable reduction in death rate and a rapid amelioration of fever and symptoms in cases of Type II pneumococcus pneumonia treated with specific antiserum, as compared with contemporaneous and comparable non-serum treated cases due to the same type of pneumococcus. During this period, no deaths occurred among 29 patients under 40 years of age, who were treated with serum before the end of the fourth day of the disease, and no cases were encountered in which bacteremia first developed, or extensions of the pulmonary lesions were first noted following treatment with serum.[6] In the three succeeding years, from June, 1932, through May, 1935, the effect of serum treatment on mortality was obviously less striking; clinical improvement was often delayed in the patients who recovered; and cases were encountered in which extension occurred, or in which bacteremia either developed or recurred following serum treatment.

TABLE 1.—MORTALITY AMONG CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA AT THE BOSTON CITY HOSPITAL.

	Serum treated.						Non-serum treated.		
	1929–1932.			1932–1935.			1929–1935.		
	Number.	Died.	Per cent.	Number.	Died.	Per cent.	Number.	Died.	Per cent.
All cases	48	11	23	38	16	42	148	76	51
Cases with sterile blood cultures	36	4	11	21	5	24	39	10	26
Bacteremic cases	12	7	58	17	11	65	53	38	72

The percentage of serum treated cases that died during the latter period was almost the same as among the non-serum treated cases (Table 1). The difference in results could not be attributed entirely to the greater incidence of bacteremic cases in the later period, since the mortality among the patients with sterile blood cultures who were treated at this time was almost the same as among non-serum treated cases. Furthermore, a number of deaths occurred among treated patients under 30 years. Nor could the differences be explained on the basis of the inclusion of cases treated with serum late in the disease or while moribund. When all patients were excluded who died within 24 hours after the first dose of serum, or who received less than 30 cc. of serum before the end of the fifth day of the disease, the differences in mortality were still great (Table 2).

Attention was then directed to the amount of serum given. The average total volume of serum per patient was only slightly less

in 1932–1935 than in the preceding period (Table 3, *A*). The total amount of antibody given each patient was then calculated, as nearly as possible, on the basis of units consistent with a Type II antibody content of 200 units assigned to Felton's standard serum F 146, or 150 units for the National Institute of Health's standard serum P 11,[7–12] and the average dose in standard units determined.* The cases treated in the years 1932–1935 now appeared to have received, on the average, only 30% of the actual amount of Type II antibody given to Type II patients during the years 1929–1932 (Table 3, *B*).

TABLE 2.—MORTALITY AMONG SERUM TREATED CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA.

(Corrected by excluding: 1, patients dying within 24 hours after the first dose of serum was given and 2, patients who received a total of less than 30 cc. of serum before the end of the fifth day of illness.)

	1929–1932.			1932–1935.		
	Number.	Died.	Per cent.	Number.	Died.	Per cent.
All cases	37	5	14	27	8	30
Cases with sterile blood cultures	29	2	7	15	2	13
Bacteremic cases	8	3	38	12	6	50

TABLE 3.—DOSAGE OF CONCENTRATED ANTIPNEUMOCOCCUS SERA USED IN CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA.

	A. Average total volume per patient (cubic centimeters).		*B.* Average total units of Type II antibody per patient, compared with standard serum (P 11 = 150 units) (thousands).	
	1929–1932.	1932–1935.	1929–1932.	1932–1935.
All cases (as in Table 1) . .	169	145	453	136
Cases with sterile blood culture	149	135	404	137
Cases with bacteremia . . .	231	157	603	135

Although the numbers of cases were small, the increased mortality during the later years appeared to be related to the marked reduction in the actual amount of protective antibody administered. This became further evident when the cases were grouped according to the total number of units of antibody injected (Table 4). Since the number of units actually received by different patients usually depended on a prearranged program based upon volume, and since the different lots of serum used varied very widely in potency, it became necessary to interpret the effect of the dosage in the individual cases. In order to arrive at some conclusion with regard to

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the optimum dosage in these cases, it was further necessary to ascertain for each case 1, whether a poor result could be attributed to the low serum dosage and 2, whether a large dose was entirely necessary when the response to serum appeared to be favorable.

TABLE 4.—MORTALITY IN SERUM TREATED CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA IN RELATION TO DOSE OF ANTIBODY AND STAGE OF DISEASE WHEN IT WAS FIRST GIVEN. (SUMMARY OF TABLE 5).

	Dose in thousand of units of Type II antibody.	Blood culture.	Number.	Died.	Per cent.
Serum first given before end of fifth day	Less than 100	Negative	15	3	20
		Positive	6	4	67
		Total	21	7	33
	100–400	Negative	17	2	12
		Positive	11	8	73
		Total	28	10	36
	More than 400	Negative	16	1	6
		Positive	6	1	17
		Total	22	2	9
	All cases	Negative	48	6	13
		Positive	23	13	57
		Total	71	19	27
Serum first given after end of fifth day	All cases	Negative	10	3	30
		Positive	5	5	100
		Total	15	8	60

For this purpose, the serum treated cases were all listed according to the corrected number of standard Felton units of antibody actually given and the total volume of serum, the day of the disease when its administration was begun, the mode and day of termination of the disease, and the extent of pulmonary involvement at the onset of therapy were noted (Table 5). The cases in which serum was first given after the fifth day of illness were listed separately and the bacteremic and non-bacteremic cases were segregated. From these data, interpreted with respect to the events that occurred in each case, it was hoped to arrive at a tentative conclusion with respect to: 1, a dosage, in terms of a standard unit, which could be considered adequate to bring about a good clinical response in the greatest number of cases without being unduly wasteful; 2, the sort of cases which require larger amounts and 3, an approximation of the number of units necessary in the latter cases.

It is necessary, first, to explain how the dosage was arranged in the various cases. During the earlier part of this work, conducted with Dr. W. D. Sutliff, an attempt was made to introduce a large amount of antiserum in a short interval. It was believed, empirically that immediate untoward reactions, particularly chills, could be

TABLE 5.—RELATIONSHIP OF DOSAGE OF SPECIFIC ANTIBODY TO OUTCOME IN CASES OF TYPE II PNEUMOCOCCUS PNEUMONIA.

A. Patients with sterile blood cultures to whom serum was first given before the end of the 5th day of illness. (a)

Type II antibody.		First	Termination of disease.				
Units (b) (thousands).	Volume (cc.).	day serum given (a).	Mode.	Day (a)	Age (years).	Lobes involved (c).	Case number (d)
-14	5	2	Died	9	52	Ru	70 (e)
18	30	4	Died	5	34	Rl Ll	71
30	75	3	Crisis	4	20	Rl	24
30	30	2	Crisis	3	24	Ll	6
44	110	5	Crisis	6	35	Rl	21
60	60	3	Died	4	40	Ru Ll	73
69	25	5	Crisis	5	14	Ru	29
70	70	4	Crisis	5	18	Rlm	49
75	75	5	Lysis	7	39	Rlm	53
75	75	4	Crisis	5	23	Ll	54
85	85	3	Lysis	5	47	Ll	44
89	105	5	Crisis	6	15	Rl	58
89	105	2	Lysis	3	50	Ru	59
90	90	4	Lysis	4	24	Ll	26
100	100	4	Crisis	5	24	Ll	32
120	40	3	Lysis	3	24	Rl	7
120	120	3	Crisis	4	43	Ll	43
135	135	3	Crisis	5	38	Rl	46
150	195	3	Crisis	4	25	Rl	27
150	150	5	Lysis	7	31	Ll	51
180	180	5	Died	6	55	Ru	78 (f)
180	300	3	Lysis	11	31	Ll	38 (e)
190	205	5	Crisis	6	23	Ll	3
221	130	2	Died	6	37	Lul	86 (h)
242	121	5	Crisis	6	39	Rl	8
244	140	2	Crisis	3	29	Ll	30
247	90	3	Crisis	4	17	Rl	48
264	220	4	Crisis	5	25	Ll	25
275	100	3	Crisis	4	14	Rl	31
285	285	5	Lysis	7	43	Ru	42
285	285	3	Crisis	5	17	Rl	50
315	105	4	Crisis	5	13	Ll	23
425	141	3	Crisis	4	31	Rl	12
435	145	5	Crisis	6	50	Ll	2
440	440	4	Crisis	6	41	Ll	40
470	150	1	Lysis	2	20	Ll	14
480	120	2	Lysis	4	40	Rl	22
495	110	2	Lysis	3	36	Ll	20
514	133	4	Crisis	5	53	Rl	1
550	200	3	Lysis	3	28	Rl	33
550	200	3	Crisis	4	29	Rl	35
569	200	3	Lysis	5	43	Rl	34
652	163	3	Crisis	4	16	Ll	18
730	162	2	Crisis	3	14	Ru	13
736	230	3	Died	7	54	Ll	63 (i)
783	261	3	Lysis	5	24	Rl	16
1100	255	5	Lysis	7	53	Rl	17
1384	346	2	Lysis	6	24	Ll	15

(a) The day of the chill or initial chest pain is considered 1st day; except for Case 60, all cases listed under *A* and *B* were admitted within 96 hours of onset.

(b) Reduced, as nearly as possible, to a value consistent with 150 units, Type II for standard serum P 11, or F 146 = 200 units per cc.

(c) R = right; L = left; l = lower; m = middle; u = upper.

(d) Cases 1 to 37 and 60 to 71 (inclusive) were treated during 1929–1932.

(e) Bacteremia after serum. (f) Chronic and acute nephritis with uremia.

(g) Serum discontinued after 72,000 units (180 cc.), blood culture positive on 5th day; further serum given on 6th day; blood culture sterile on 7th day. Subcutaneous pneumococcus abscesses incised later.

(h) Delirium tremens; serum given through 4th day; blood culture positive on 5th day.

(i) Delirium tremens.

B. Bacteremic patients to whom serum was first given before the end of the 5th day.

Type II antibody. Units (thousands).	Volume (cc.).	First day serum given.	Termination of disease. Mode.	Day.	Age (years).	Lobes involved.	Case number.
25	25	4	Died	5	28	Ruml	76
30	60	5	Died	6	53	Ruml	82
53	105	4	Died	38	35	Ruml	83 (j)
58	115	5	Lysis	9	60	Rul Ll	55
70	140	4	Died	8	20	Rlm	80
98	190	3	Lysis	7	37	Ll	57
123	135	3	Crisis	5	58	Rl	47 (j)
147	225	4	Died	13	18	Rl	84 (k)
150	150	3	Crisis	4	44	Ll	39
153	305	3	Died	6	48	Ru	68
240	150	3	Died	8	21	Rl Ll	74
248	155	3	Lysis	4	27	Rum	41
255	255	3	Died	8	63	Ll	77
278	105	4	Died	9	48	Lu	67
295	230	2	Died	4	50	Rl Ll	65 (l)
358	130	5	Died	5	66	Ll	66 (i)
360	360	2	Died	8	72	Ll	72 (m)
550	200	3	Lysis	8	36	Rl	36
591	298	3	Lysis	5	19	Lu	19
619	225	4	Crisis	5	28	Ll	28
795	265	4	Lysis	?	37	Rl Ll	37 (n)
1366	479	4	Lysis	7	5	Ll Rm	5
1935	430	5	Died	8	40	Rl Ll	69 (i)

C. Patients to whom serum was first given after the 5th day of illness.

Type II antibody. Units (thousands).	Volume (cc.).	First day serum given.	Termination of disease. Mode.	Day.	Age (years).	Lobes involved.	Case number.
Cases with Sterile Blood Cultures:							
13	28	9	Lysis	10	44	Rl Ll	45
60	120	6	Lysis	8	31	Ll	56
73	145	11	Died	13	35	Rl	81
75	75	6	Died	9	55	Rl	60
90	90	6	Lysis	8	18	Ru	52
183	61	6	Lysis	8	33	Ru	9
345	115	6	Crisis	7	13	Ll	4
375	125	8	Crisis	9	57	Rl	11
531	177	7	Crisis	8	32	Rl	10
675	225	7	Died	8	34	Ru Lul	61
Cases with Bacteremia:							
26	15	7	Died	7	49	Ru Ll	85
53	105	8	Died	10	34	Ll	79
105	35	6	Died	7	37	Ruml	64
186	186	10	Died	14	25	Rl Ll	75
195	65	22	Died	23	65	Ruml	62

(j) Empyema.

(k) 13,000 units 4th day; 134,000 units 5th day; blood culture sterile 6th day; bacteremia later recurred and lesion extended to Rm Ll.

(l) Delirium tremens, fractured skull, operation.

(m) Serum given (about 75,000 units daily) for 5 days; bacteremia cleared and recurred twice.

(n) Hemolytic streptococcus empyema and otitis media, erysipelas.

reduced or avoided by giving a small initial volume followed by increasing amounts up to 50 cc. Most of the cases, therefore, were given an initial dose of 5 cc., a second dose of 25, and 3 or 4 more doses of 40 to 50 cc. of the serum concentrates at intervals of 2 hours. Further doses were given after a lapse of 8 to 12 hours, the amounts and intervals usually being gauged by the condition of the patient. In the last 3 years smaller initial amounts, with a total of between 75 and 150 cc., were given, and the further treatment was not controlled in every instance. Throughout this work, changes in dosage were made for convenience or because the condition of the patient warranted it. Thus, if the first 2 or 3 injections were given late at night, an interval of 8 to 10 hours was allowed to lapse before the subsequent dose. If, in the morning, the patient was found to be afebrile or much improved, the remaining doses were reduced or omitted.

With this scheme of dosage in mind, let us consider first the bacteremic cases (Table 5, *B*) since, as judged from mortality rates, these may be assumed to be the severest cases. Of the 6 patients with bacteremia who received less than 100,000 units only 2 recovered. Since, in each of these 2 cases, an interval of 4 days elapsed between the time serum was given and the day recovery began, it is fair to assume that this recovery was probably not related to the serum therapy. Among the 11 bacteremic cases in which the total amount of antibody given was between 100,000 and 360,000 units there were 3 survivals. In each instance, clinical improvement seemed clearly related to the time of antibody administration in these 3 surviving patients. The amounts of serum were given to these patients according to a prearranged schedule of dosage based on volume, and no further serum seemed necessary. Of the remaining 6 bacteremic patients, each of whom received more than 500,000 units, only 1 died. The 5 patients who recovered were given between 465,000 and 619,000 units of Type II antibody within about 10 hours, according to schedule; the additional amounts being given because the fever and acute symptoms were not satisfactorily improved and being gauged according to the condition of the patient. In only one instance (Case 5) did the condition of the patient warrant the further use of large amounts of serum.

The deaths among the bacteremic cases, except in Cases 74, 67, 66 and 69, occurred in patients treated with serums of low potency, equivalent to 1000 or less standard units of antibody per cubic centimeter of serum (see Tables 5 and 6). In these 4 cases, other reasons militated against the full efficacy of the antibody: a hemolytic streptococcic "superinfection" in Case 74; a spread of dosage with a small total amount in Case 67, a patient with auricular fibrillation; and treatment begun on the fifth day in severely alcoholic patients with delirium tremens in Cases 66 and 69. The remaining fatal bacteremic cases may now be considered in the order that they appear in Table 5.

In the first 4 patients, less than 100,000 units were used and no effect was observed either on the bacteremia or on the clinical symptoms. In Case 84, all of the serum (174,000 units contained in 225 cc.) was given before the end of the fifth day and the blood cultures were sterile during the following 3 days. On the eighth day bacteremia recurred, and the pneumonia extended throughout the previously uninvolved lobes on the same side and also to one lobe in the opposite lung. Although the blood cultures taken 2 days later were sterile, the patient died. There was bilateral empyema at autopsy and the heart's blood culture was sterile. In Case 68, the first 135 cc. of serum given on the third day contained the equivalent of 68,000 units. The blood cultures on each of the 3 succeeding days were all sterile. Death occurred on the sixth day, after about 30,000 units had been given each day. The events in this case were practically duplicated in Case 77, except that 150 cc. of serum equivalent to 150,000 units of antibody were

TABLE 6.—RELATION OF DOSAGE OF TYPE II ANTIBODY TO BACTEREMIA AND OUTCOME IN CASES DISCUSSED IN TEXT.

Case		Day of disease.										
		1	2	3	4	5	6	7	8	9	10	
5	Blood culture				+	+, O	O	O, C	O			
	Antibody, cc.				30	132	184	103	13			
	Units (× 1000)				90	396	552	309	37			
15	Blood culture		O, O, O	O	O	L						
	Antibody, cc.		100	80	81	85						
	Units (× 1000)		400	320	324	340						
19	Blood culture			+, +	O	O	O, L					
	Antibody, cc.			70	115	73	40					
	Units (× 1000)			135	230	146	80					
36	Blood culture				+, +	O	O	O, L				
	Antibody, cc.				110	90						
	Units (× 1000)				283	267						
38	Blood culture		O				+		O		O	Lysis
	Antibody, cc.			120				65	30	55	30	11th
	Units (× 1000)			72				39	18	33	18	day.
63	Blood culture			O	O			D				
	Antibody, cc.			120	110							
	Units (× 1000)			384	352							
67	Blood culture			+	+	O		O	+	+, D	O	
	Antibody, cc.				45	30	30					
	Units (× 1000)				114	82	82					
68	Blood culture			+	O	O, O	O, D					
	Antibody, cc.			135	65	65	40					
	Units (× 1000)			68	32	33	20					
69	Blood culture			+	+	O	D					
	Antibody, cc.			30	200	200						
	Units (× 1000)			135	900	900						
72	Blood culture		+	O	+	O		+	D			
	Antibody, cc.		30	75	75	90	60	30				
	Units (× 1000)		30	75	75	90	60	30				
74	Blood culture			+	O	O	*		D			
	Antibody, cc.			150								
	Units (× 1000)			240								
77	Blood culture			+	O				D			
	Antibody, cc.			150	45	30	30					
	Units (× 1000)			150	45	30	30					
80	Blood culture				+			+	D, +			
	Antibody, cc.				80	60						
	Units (× 1000)				40	30						
83	Blood culture				+							
	Antibody, cc.				85	20		L	Empyema			Died
	Units (× 1000)				43	10						38th
86	Blood culture	O				+	D	+				day.
	Antibody, cc.		60	60	10							
	Units (× 1000)		102	102	17							

Blood culture: + = Growth of Type II pneumococci;
O = Sterile;
Cultures after death are from heart at autopsy.
Units = reduced to standard; F 146 = 200 units per cc.
C = crisis L = lysis D = died
* sputum culture = streptococcus hemolyticus; no pneumococci.

given on the first day of treatment and death occurred on the eighth day. Case 65 was in a patient admitted to the hospital with alcoholism, delirium, a fractured skull and other injuries. The pneumonia was first recognized 2 days after a bone flap had been done and was thought to have begun after the operation. In this patient, blood cultures taken before each of 9 injections of serum, given over a period of 36 hours and up to the time of death, showed an increasing bacteremia. In Case 72, 30,000 units of Type II antibody were given on the second day and from 60 to 90 thousand units injected daily during the next 5 days. Daily blood cultures were alternately sterile and positive, and death occurred on the eighth day. The course of bacteremia in relation to the dose of antibody in some of these cases is noted in Table 6.

The bacteremic patients who were treated after the fifth day of illness all died (Table 5, *C*). In 3 of these cases death occurred within a few hours after the first dose of serum was given. In the 2 patients who survived longer than 24 hours after the initial injection, the bacteremia was not affected.

Summarizing the observations in the bacteremic cases, it appeared that 1, doses of serum containing less than the equivalent of 100,000 standard units had no effect on the course of the disease at any time; 2, larger doses were ineffective when treatment was begun on or after the fifth day of illness; 3, when given before the fifth day a dose equivalent to about 150,000 units usually rendered the blood stream free of pneumococci but only temporarily; 4, while an occasional patient was completely relieved of symptoms following a total dose of less than 350,000 units, most cases required larger amounts up to 500,000 units to keep down the bacterial invasion; 5, when a total of less than the equivalent of 300,000 standard units was given, the bacteremia tended to recur and death ensued; 6, a total dose of more than 300,000 units was most effective when given in a short space of time, but when the dose was spread over more than 2 days, the bacteremia tended to recur in spite of repeated injections of serum.

The situation was different among the cases in which the blood cultures, taken before the initial injection of serum, were sterile. There were only 6 deaths among 40 patients to whom serum was first given before the end of the fifth day. Let us consider these fatal cases in the order in which they are listed in Table 5, *A*.

In Case 70, an initial injection of 14,000 units was followed by a reaction consisting mainly of dyspnea and slight cyanosis. The patient refused further injections. He later developed bacteremia and died. Case 71 was an Italian patient who could not speak English and who was moribund at the time of admission to the hospital. As far as it was possible to ascertain, his history suggested an illness of 4 days' duration. He died within a few hours after the first dose was given. At autopsy there was a thick fibrinopurulent empyema and an organizing pleuritis which indicated an illness of much longer than 4 days duration. Case 73 was a colored patient with bilateral lung involvement to whom serum was first given on what was considered to be the third day of illness. He was obviously failing rapidly at the time, but survived about 18 hours, during which time 5

doses of serum were injected. Case 78 was a patient with acute nephritis and uremia. The blood non-protein nitrogen level was 140 mgm. % on the fifth day of the pneumonia, when the first dose of serum was given. He died 24 hours later. Case 86 was a patient severely ill with involvement of the entire left lung, delirium tremens and leukopenia. Treatment with serum, on what was thought to be the second day of the pneumonia, and later with pentnucleotide failed to bring about any improvement. Bacteremia developed on the fifth day, after more than 200,000 units of antibody had been given on the preceding days. He had empyema at autopsy. Case 63 was also a chronic alcoholic patient who, in addition, had a history suggesting chronic tuberculosis. He was given a total of 736,000 units of antibody before the end of the fourth day, without apparent effect. He died 3 days later.

Among the 34 patients who recovered, the alleviation of fever and acute symptoms occurred in 22 cases within about 24 hours after the first injection of serum. In each of these cases the amount given was that decided upon beforehand and little or no further serum was given. In 10 other patients complete relief of acute symptoms was not attained until the second day after the first dose was given. Only one of these patients, Case 40, appeared sufficiently ill to warrant the use of large doses beyond the amount originally prescribed. The 2 remaining patients, Cases 38 and 15, were acutely ill for more than 3 days after serum treatment was begun.

Case 38 was a woman who miscarried a 5 months' fetus early in her disease. She received 72,000 units of Type II antibody on the third day of her illness. She was only partly improved but no further serum was given until the seventh day when a blood culture, taken on the previous day, was reported positive. She was then given doses of from 20 to 40 thousand units of antibody daily for 4 days. The bacteremia cleared rapidly but recovery was further delayed by the occurrence of subcutaneous pneumococcic abscesses. In Case 15, doses of over 300,000 units of Type II antibody were given daily for 4 days but marked improvement was not apparent until the last day of treatment (Table 6).

Among the 10 non-bacteremic patients treated after the fifth day of illness (Table 5, *C*), there were 3 deaths. This number of deaths corresponds to the death rate observed in non-serum treated cases with sterile blood cultures (Table 1). None of these fatal cases showed any obvious improvement after serum treatment. In the recovered cases, though symptoms were alleviated within 24 or 48 hours after serum therapy, it is difficult to consider a causal relationship at such a late stage of the disease. Recovery in these cases occurred on or after the seventh day of illness.

Summarizing the results noted in the non-bacteremic cases, it appeared that: 1, cases treated before the end of the fifth day usually responded with a prompt and permanent reduction of fever and alleviation of symptoms of the acute disease; 2, such a response occurred after any amount of antibody over 30,000 standard units, but in over half of the cases more than 150,000 units were actually

given; 3, the larger amounts of antibody were given, in most instances, because of the high potency of certain lots and because dosage was prescribed by volume; (4), fatalities among non-bacteremic cases occurred almost entirely in patients with other complicating conditions, including delirium tremens, or where it seemed likely that the patients were ill for a longer period than that suggested by the anamnesis—at any rate, these patients were *in extremis* when the serum was first given; 5, it is difficult to evaluate the effect of serum in the cases treated after the fifth day of illness, but no obvious benefit seemed to follow its use; and 6, in 2 of the 3 patients who developed bacteremia after serum treatment was begun, this therapy had been discontinued after less than 75,000 units had been given; in the third patient, who had delirium tremens and leukopenia, no effect was apparent from 220,000 units given over a period of 48 hours.

On the basis of the observations in these non-bacteremic cases, it seems fair to assume that recovery in almost all of the cases was related to the serum therapy when that was given before the end of the fifth day. It also seems reasonable to suppose, from a consideration of the manner in which the dosage was arranged, that the greater amounts were largely redundant. These large amounts were, in almost all instances, contained in the volume originally prescribed and these large numbers of units of antibody were due to the potency of the particular lots used. When less potent antiserums were given, the total amount of antibody, in terms of units was smaller, but it was nevertheless effective. This was also apparent when less than the full prescribed dose had been given and an interval was permitted to elapse. In many such instances no further serum was given because it was considered unnecessary.

In the light of these considerations it seems reasonable to suppose that 100,000 to 150,000 standard units of Type II antibody should prove effective in bringing about a favorable, rapid and permanent response in all but a small number of cases, provided that this amount of antibody is given before the end of the fifth day and the blood culture is sterile before the first dose is given. If this blood culture shows a growth of pneumococci, it seems necessary to give another 150 to 200 thousand units, and even more antibody may be required, persistence in treatment being essential. Optimum results seem to follow administration of the larger amounts when they are given within 24 to 36 hours after treatment is first begun. It seems unwise to permit more than 12 hours to elapse without giving more antibody to a patient in whom the fever, elevated pulse rate, or delirium persist or who otherwise looks acutely ill, unless it is ascertained that the symptoms are attributable to a process other than the Type II pneumococcus pneumonia. The patients with bacteremia who are first treated on or after the fifth day of illness apparently derive no benefit from the serum. The impres-

sion has been gained that some of these Type II bacteremic patients appear to decline more rapidly after treatment with serum, when that therapy is initiated late in the disease.

Comment. The goal of all therapy is primarily the saving of life and secondarily the complete and expeditious relief of symptoms. Mortality rates, particularly in a disease like pneumonia, are dependent on many factors in the host and in the invader. Large numbers of cases, therefore, must be treated and thoroughly analyzed along with comparable untreated cases before the life-saving property of a therapeutic agent can be justly evaluated. Pending the accumulation of sufficient data, the best early guide to the efficacy of a specific remedy is the rapid and complete alleviation of acute symptoms, in uncomplicated cases, after this remedy is administered. Such rapid and complete symptomatic relief has occurred in a large proportion of cases of pneumococcus Type I pneumonia when adequately treated early in the disease with Type I antipneumococcus serum. With respect to Type I cases, also, the efficacy of specific serum therapy is supported by a sufficient body of mortality figures. Much of the recent success in the use of this agent is probably attributable to those advances made in the production and concentration of Type I antipneumococcic serum which have made it possible for physicians to give large amounts of antibody with comparative ease.[8]

The report of Finland and Sutliff[6] on the treatment of pneumococcus Type II pneumonia with specific antibodies indicated that very similar symptomatic improvement could be obtained and, as far as could be judged from the small number of cases treated, the mortality could be influenced to almost the same extent as in Type I cases. During the period covered by that report, full cognizance was taken of the observations of Park and Cooper[2,3] that large amounts of antiserum are needed to establish a balance of antibody in the blood of patients with Type II pneumococcus pneumonia. In almost all cases, therefore, the serums used were selected because of their high potency in Type II antibody, and large volumes of these serums were given. During the following 3-year period, serums were used which were distributed for use in both Type I and Type II cases and had a considerably lower content of Type II antibody. During the latter period each patient received an average of only three-tenths as much antibody as was given to the cases included in the earlier report. It was felt that this drastic reduction in the actual amount of antibody given accounted, in large part, for the sharp increase in the percentage of deaths among the serum-treated cases, reaching a figure almost equal to the mortality among non-serum-treated cases. The clinical effects in the recovered cases also were not uniformly satisfactory.

The importance of having a uniform standard serum for the titration of antipneumococcus serums is evident from the data

presented. The need for such a standard has long been recognized. It was first put into use for the titration of concentrated Types I and II antipneumococcus serums by Felton[9] and recommended for international use in a specially prepared dry form by Hartley and Smith.[11,12] Such a standard is indispensable until such a time when it will be possible to titrate the biologic potency of antipneumococcus serum adequately and uniformly without the introduction of the variables in the mice and in the virulence of living pneumococci. Any discussion of dosage in terms of units of antibody becomes meaningless unless full cognizance is taken of the manner in which the antibody is titrated and unless some acceptable standard has been used for comparison.

The importance of making blood cultures before beginning serum therapy may again be emphasized. This is obvious from the data presented. Almost half of the untreated cases of Type II pneumonia in three large clinics have been found to yield positive blood cultures, and the prognostic significance of this feature is readily apparent from the differences in mortality noted in bacteremic and non-bacteremic cases in each of these series.[5,20,21] Its further importance as a guide to dosage has been noted by earlier observers[1–5] and is apparent from the data presented here. The prevention of the appearance of bacteremia has also been shown to depend on the administration of adequate amounts of antibody early in the disease.

The possibility of maintaining a balance of antibody in some cases of Type II pneumonia with unconcentrated serum of low potency was noted by Cole.[1] Finland and Sutliff[13] attempted to define the dose of Felton's serum effective in pneumonia on the basis of the cutaneous reactions with homologous type-specific polysaccharides. On reëxamining the data in the Type II cases, taking into account what has been said regarding the units of antibody, it appeared that in one instance (Case 6) the equivalent of 30,000 standard units had been given and the remaining cases had received between 100 and 160 thousand units before the positive cutaneous reactions were first elicited. With one exception (Case 5), these cases had sterile blood cultures before the antibody was given. Lord and Persons[14] failed to establish a balance of protective antibody in one Type II case with less than 200,000 Felton units, and succeeded in doing so in a second patient given more than that amount before the sixth day. Park and Cooper[3] calculated more than 500,000 units would have been necessary to accomplish this result in two of their bacteremic cases.

The use of various tests for an excess of antibody in the patient has not yet been carried out sufficiently to warrant their unqualified use as a guide to the control of dosage in Type II cases. Several such tests have been suggested including: 1, the rapid macroscopic agglutination test as used by Sutliff;[15] 2, the stained-slide microscopic agglutination test of Sabin;[16] and 3, the skin test with the

homologous type-specific polysaccharide (Tillett and Francis[17]), as adapted to the control of dosage in Type I cases by Francis.[18] The latter test is probably the most desirable since it is a tissue reaction. Occasional patients, however, fail to give the characteristic response regardless of complete recovery with an excess of antibody, and others fail to recover after a positive test has been elicited.[13] It is felt that the blood culture, the presence of fever, elevated pulse rate and evidences of "toxemia" and the response to earlier doses, if sufficiently large, probably serve as the most useful and practical guides for continuation of antibody therapy in the individual case.

Based upon the observations in the present cases, a tentative plan of dosage based upon a standard unit is proposed which may be expected to give the optimum effect on the mortality rate in any group of cases and on the clinical condition of the individual cases. This dosage may seem somewhat wasteful but appears to be warranted by the data at hand, and takes into account the danger of giving smaller amounts to the severer cases, in which valuable time may be lost. It must be kept in mind, however, that these recommendations are based on a comparatively small number of cases and may require modification as more data become available.

The experiences of the past few years with Type I cases, both in this country and in Great Britain, have shown quite clearly the advantage of having potent concentrated antiserum which enables physicians to give large amounts of specific antibody in a small volume and with a comparatively small amount of total solid. It is desirable, therefore, to do the same for Type II cases. Since concentrated serums of high potency in Type II antibody are comparatively difficult to make with great regularity, it would seem helpful to withhold from distribution for use in Type II cases serums of low potency in antibodies for this type. About 1500 standard units per cubic centimeter would be a reasonable minimum, and higher concentrations than this are preferable if they can be attained without excessive amounts of total solid. With such serums, physicians would be more inclined to treat their patients adequately.

The occurrence of the so-called "zone phenomenon" in the interaction of pneumococcus antigens and antibodies raises the question of a possible harmful effect of excessive dosage. Such zone phenomena have been demonstrated for agglutination, precipitins, phagocytosis and passive protection of mice, but have not been observed in the results of treatment in human cases (see Ward[19]). The test-tube experiments do not take into account the large reservoir of neutralizing material which is present in the infected lung.

The results of therapy have been considered here primarily from the point of view of dosage. Other features of serum therapy have been considered elsewhere.[6] A more detailed analysis of all the Type II cases is included in a separate communication.[21]

Conclusions. Clinical attempts to determine the proper dose of serum in the treatment of cases of pneumococcus Type II pneumonia have emphasized the importance of having a uniform standard with which the potency of various lots of Type II antipneumococcus serums can be compared. The adoption of an international standard, as proposed by Hartley and Smith, is highly recommended.

A tentative plan of dosage for Type II cases is offered, which is based upon observations on the effect of various amounts of antibody:

1. When a diagnosis of Type II pneumococcus pneumonia is made, an amount of Type II antibody equivalent to 100,000 or, preferably, 150,000 units of the proposed standard serum should be given to the patient in as short an interval as is consistent with the avoidance of untoward reactions.

2. An additional 200,000 units should be given to all cases showing Type II pneumococci in the blood culture. This amount should also be given in as short an interval as is consistent with safety and even in spite of apparent improvement in the patient's condition.

3. Additional amounts of 50,000 to 100,000 units should be given at intervals of 6 to 12 hours in all cases until the fever and other acute symptoms are relieved, or until it is shown that these symptoms are not due to the Type II pneumococcus pneumonia.

4. After treatment is once begun, it is unwise to permit an interval of more than 12 hours to elapse without giving further serum, unless the patient is relieved of fever and serious symptoms.

Treatment with antibody beginning after the end of the fourth day of illness is probably of no benefit, except possibly in non-bacteremic cases, and then only if it is begun during the fifth day.

The results of blood cultures are the most important guide to serum dosage in addition to being of great prognostic significance.

The interests of physician and patient are served best if only serums of high potency in Type II antibody are released for treatment of patients with pneumonia due to this type.

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EPIDEMIC PLEURODYNIA.

("DEVIL'S GRIP") IN CINCINNATI.

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ELEVEN cases of epidemic pleurodynia occurring among the personnel of this hospital are described in this report. The first case was seen on June 18 and the last on September 25, 1935. They are typical of cases reported in the literature as well as of numerous other cases seen by physicians in Cincinnati during the same period.[1]

Outbreaks have been reported from the Eastern and Southern States of this country since the disease was first noted here in 1888.[2,3,4] Daae and Homann, of Norway, are given credit for the early, if not the first, description of the disease in medical literature.

As described in the literature, the disease is said to occur in paroxysms lasting 24 or more hours. These are characterized by

sudden onset of excruciating pain in the chest or epigastrium, the pain being aggravated by deep breathing or movement of the trunk; often a chill; fever of 100° to 105° F.; tenderness, frequently persistent, and usually over the site of pain; a normal white cell count or leukopenia; and the absence of important pleural or pulmonary physical findings. It occurs during the summer months, attacking healthy young people of either sex, more commonly children, and frequently several members of the same family. It may subside after one paroxysm, or there may be one or more recurrences after a period of 24 to 30 hours of comparative comfort. Recovery is usually prompt and complete, although Churchill[5] reports that the recovery in his patients was slower than the severity of the acute symptoms would seem to warrant.

The etiology of the disease is not known. Small[6] described a protozoan organism within the erythrocytes of 2 patients with the disease. Failure of other workers to confirm his findings should not cause a careful blood study to be omitted.

The nature and location of the pathologic lesions are unknown. It has been suggested that they might be a myositis of the chest wall and back.[4] However, no microscopic studies of the apparently affected muscles have been reported.

The outbreak described in this paper is apparently the first one in the Middle West. A microscopic study of the muscles was made in 1 patient. Since the patients comprising the reported group were interns and nurses, an excellent opportunity for observation was had. For these reasons this communication is made.

Description of Cases. Of the 11 cases diagnosed as epidemic pleurodynia, 8 were admitted to the hospital and 3 were treated as office patients. This description will be confined to the former, although the latter were similar, but could not be observed so closely.

Of those admitted to the hospital, 5 were nurses, 2 interns and 1 the wife of a physician. There were 7 women and 1 man, their ages ranging from 18 to 25 (average 21). All had been in good health until the onset of their present illness.

Prodromal Symptoms. Four of the patients gave a history of feeling tired and "dragged out" for 2 to 7 days prior to the onset of acute symptoms; 2 had vague, generalized abdominal cramps not associated with nausea, vomiting, or diarrhea.

Onset. In half of the group the onset was abrupt with excruciating pain in the epigastrium and along the anterior costal margins, the pain being aggravated by movement or deep breathing; in the remainder the pain was minimal at first but gradually grew worse, reaching a maximum of intensity in 4 to 12 hours after its first appearance.

Symptoms. Pain: This was the most prominent feature of the disease. Inspiratory chest pain, described as being cramp-like in character, was the most common type, although in 1 patient the

pain associated with the first paroxysm was epigastric, being increased more by movement of the trunk than by deep inspiration. In 4 the pain was localized to the left chest and hypochondrium with each paroxysm. In the others the pain alternated with each side of the chest in the succeeding attacks. In 1 instance, right lower quadrant abdominal pain preceded the appearance of pain in the right chest by 4 hours. Three of the group were entirely free of pain between paroxysms; the others had slight pain on deep inspiration. Tenderness over the site of pain, although hard for the patient to localize, was a constant finding even between paroxysms. It did not persist for longer than 1 day after the termination of the acute symptoms.

Fever: The fever usually followed the pain, there being a lag of a few hours between the onset of the pain and the fever, while the reverse was true at the end of the paroxysm. The "pain-fever" relationship, however, was very close. It was the predominant symptom in each recurrence except one in which the patient's third paroxysm of pain was not accompanied by fever. The elevations in temperature ranged from 99.4° to 104° F. The pulse rate increased in proportion to the fever.

General Symptoms. Aside from the epigastric and right lower quadrant abdominal pain and the prodromes already mentioned, symptoms referable to the abdomen and gastro-intestinal tract were not noted. All of the patients except 1 felt well during the interval between attacks. Headache, generalized muscular aching, weakness, and loss of appetite were not prominent symptoms. None of the patients complained of cough, and none gave a history of recent acute respiratory disease.

Number of Attacks or Paroxysms. Five of the patients had 3 paroxysms; 1, 9; 1, 2; and 1, 1. Most of the attacks were sharply defined, so much so that in many cases the time of onset of the succeeding ones could be fairly accurately predicted. The third attack was always the most severe.

Physical Findings. During the height of an attack the skin was flushed, moist and hot, but no skin eruptions, aside from herpes labialis, were observed. Tenderness over the site of the pain was a constant finding and protective splinting of the affected chest was common. Persistent, fine râles at the base of the axilla were noted in 1 patient. Aside from this instance, no pulmonary or pleural signs were detected. One patient, whose illness was similar in all respects to the others reported here, and on whom a biopsy of a muscle of the chest wall was taken, developed a pleural friction rub 5 days after his discharge from the hospital. A hematoma which had developed in the wound may have played a part in the production of this physical sign. However, his case is not included in this series.

Laboratory Findings. The leukocyte count averaged 7400. White cell counts taken after the fifth day of the illness on 3 patients averaged 5000, while counts on the other 5, taken within the first two days of the illness, averaged 9900. The neutrophils varied from 54 to 78% and in no case was eosinophilia noted or were intracellular sporozoa found. The urine was negative. Blood cultures taken in 6 cases were sterile.

Muscle Biopsy. A section of the apparently affected latissimus dorsi muscle was taken from one of its slips of origin on the lower chest wall. Cultures of the tissue were sterile. Microscopic study revealed no morphologic change.

Roentgen Ray Examinations. All patients had had a Roentgen ray examination of the chest within 6 months of the time of their admission to the hospital. Five, as part of a yearly physical examination, had had the examination 3 weeks prior to their illness. Further examinations were made during the illness and were repeated on an average of 6 weeks after discharge. No change in the findings was noted during these periods.

Duration. The average duration of the illness as judged from the first attack of acute pain and fever until the termination of the last paroxysm was 5 days.

Convalescence. Six of the patients experienced occasional fleeting chest pains for 4 days after discharge, stating that they felt well after these had disappeared. One patient had chest pain, lasting from a few minutes to as long as 1 hour, for a month. She did not feel badly otherwise. Another experienced similar pain for 2 months and felt tired for 3 weeks following her discharge. When last seen, late in September, 1935, all of the patients were free from symptoms and in good health.

A Typical Case. Dr. Nina A., a woman intern, aged 24, developed pain of an inspiratory nature in the left side of the chest at noon, July 19, 1935. She was seen 2 hours later, at which time the temperature was 99° F. Examination of the chest was negative aside from tenderness over the lower left anterior costal margin. Six hours after the onset the temperature was 102° F., the pulse was 110 and the respirations 25. The pain was very severe, being aggravated by movement or inspiration. Her past history was not remarkable. She had been in good health until the present illness. Routine Roentgen ray examination of the chest 2 weeks previously had been negative. The first paroxysm of pain and fever lasted for 36 hours. Following this was a 24-hour interval of comfort. At the end of this period a second paroxysm lasting 24 hours occurred. This was followed by a comfort interval of 30 hours, then a third paroxysm lasting 24 hours (Chart I). The pain was the most severe in the last recurrence. At the end of the third attack she felt quite well and remained so until discharge, 5 days later. Repeated examinations of the chest were negative. A Roentgen ray film of the chest on the day of admission showed no change from the one taken 2 weeks previously. The urine was negative. A blood culture taken, July 25, was sterile. The leukocyte count on the second day of the illness was 8600. The blood smear showed 70% neutrophils, 28% lymphocytes and 2% monocytes. On July 27, a small section of the latissimus dorsi muscle was removed from one of its slips of origin in the left

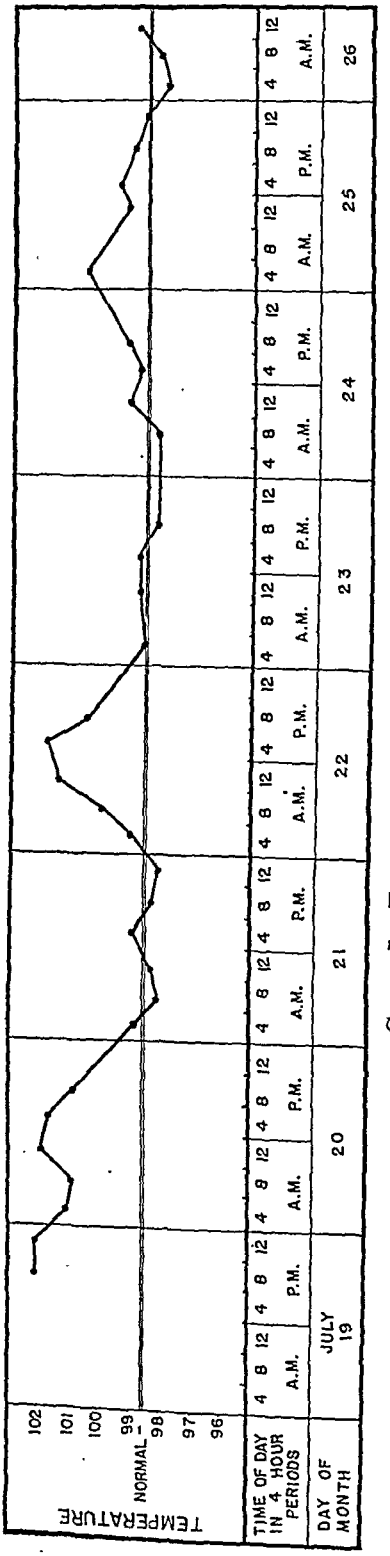


CHART I.—Temperature in the case reported.

chest wall. Cultures of the muscle were sterile. Microscopic studies did not show any morphologic changes.

The patient was discharged from the hospital after 12 days, and when last seen, September 20, 1935, she was in good health. A Roentgen ray film of the chest at this time showed no change from those taken previously.

Summary. Eleven cases diagnosed as epidemic pleurodynia are reported. They were apparently a part of an epidemic occurring in this area.

In this small series of cases, the majority had 3 recurrences, the third one being the most severe. One-half of the patients had prodromal symptoms and a gradual onset. The pain preceded the fever, but the "pain-fever" relationship was close. Tenderness over the site of pain did not persist after the acute symptoms had subsided. The pain was described as cramp-like in character. There were no important pleural or pulmonary findings either on clinical or repeated Roentgen ray examinations. Leukocyte counts in 5 cases taken during the first 2 days of the illness were normal. Those taken after the fifth day (3 cases) were low.

This is the first reported outbreak of the disease in the Middle West.

Microscopic study of the apparently affected muscle of 1 patient did not show any morphologic changes. This is the first such study to be reported and should be repeated on a large number of patients.

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EPIDEMIC MYALGIA OR PLEURODYNIA IN SOUTHWESTERN OHIO.

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In this portion of the United States, epidemic pleurodynia was first diagnosed in the summer of 1935. The initial recognition came from at least four independent sources; two hospital physicians, a general practitioner and a district physician of the Cincinnati Health Department. Through newspaper accounts of "devil's grip,"

the clinical picture was subsequently so well publicized that laymen often diagnosed the typical cases before summoning a physician, or did not summon one at all.

It has been stated[1] that epidemics of this condition were first recorded in Iceland (1856) and Norway (1872), and also in England, Denmark, Sweden, Finland, Germany and Portugal. Local names are frequently given to the disease, such as "Bornholm's Disease" after the Island of Bornholm, and "the Bamle disease" in Norway. In England the term "epidemic pleurisy" is popular. "Epidemic myalgia," the name preferred by some,[1] is based on the assumption that the pain has its origin in the muscles of the chest and abdomen; "epidemic pleurodynia" is the name which seems to have the most general use in the United States at the present time. The American reports of epidemic pleurodynia are summarized in Table 1. When the disease was first recognized in Cincinnati during the summer of 1935, the Health Department requested that physicians report it on the regular communicable disease forms. The total of 282 cases is probably much less than the actual incidence of the disease because so many were not seen by physicians. Chart I gives the onset of reported cases during the weeks of the epidemic. Communications with several private hospitals and practising physicians show that the disease also appeared in the nearby portions of Ohio and northern Kentucky.

TABLE 1.—PREVIOUS AMERICAN EPIDEMICS.

Author.	Title of article.	Location.	Year of epidemic.	Season.	No. of cases.
Dabney[2]	Account of an epidemic resembling dengue which occurred in and around Charlottesville and the University of Virginia, in June, 1888	Virginia	1888	Late spring and early summer	29 and "at least as many more."
Reilly[3]	An epidemic of intercostal neuritis	New York City	1899	Late spring and early summer	14
Reilly[4]	An unusual pain syndrome associated with the present wave of influenza	New York City	1921	Late spring and early summer	"Group.
Payne and Armstrong[5]	Epidemic transient diaphragmatic spasm	Virginia	1923	Summer	27
Hanger McCoy and Frantz[6]	An epidemic of mild fever of unknown nature	New York City	1923	Summer	16
Greene[7]	Epidemic pleurodynia?	New York City	1923	Summer	141
Torrey[8]	Epidemic diaphragmatic pleurodynia or "Devil's Grip"	Philadelphia, Pa.	1924	Summer	4
Churchill, Landis and Glusker[9]	An epidemic of undetermined nature: dengue?	Cape Cod, Mass.	1926	Summer	50
Richter and Levine[10]	Epidemic pleurodynia	Boston, Mass.	1933	Summer and early fall	24
Crone and Chapman[11]	Epidemic pleurodynia	Boston, Mass.	1933	Summer and early fall	30
Callaway[12]	Epidemic pleurodynia	Durham, N.C.	1934		29

This study is based only on the 282 cases reported from Cincinnati. Although the material is primarily epidemiological in nature,

some of the reporting physicians sent in clinical and laboratory data which are of interest.

Epidemiologic Aspects. The summer weather of Cincinnati tends to be warm and moist. There was a little more rain in the summer of 1935 than normal, and the average temperature was a little elevated above normal, but the deviations were not striking.

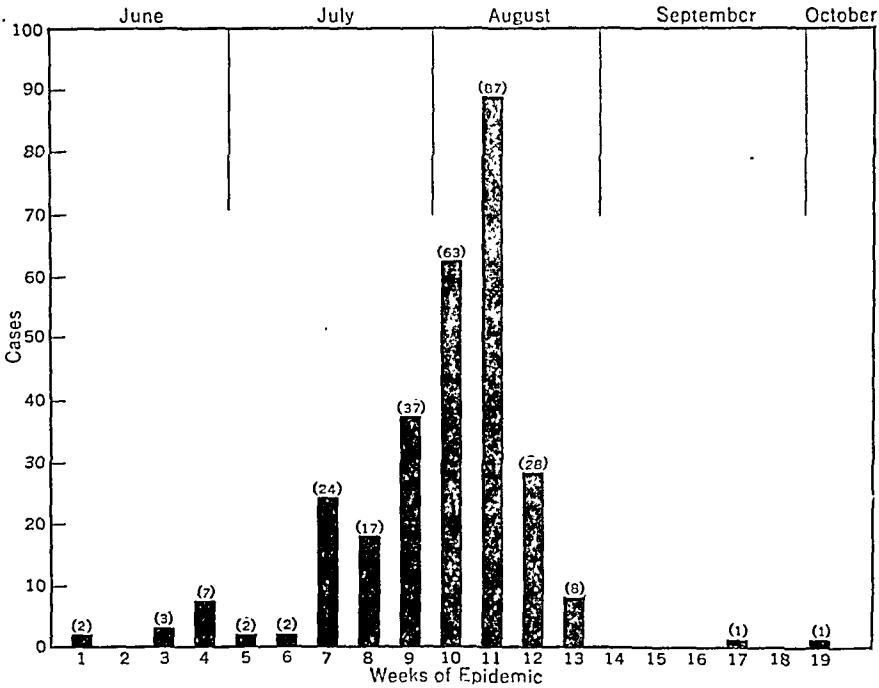


CHART I.—Occurrence of epidemic pleurodynia in Cincinnati by weeks.

Distribution between the sexes is approximately equal; of the 282 cases, 145 (51.4%) occurred in males, and 137 (48.6%) in females. (In the population as a whole there is a slight preponderance of females.)

The colored and white races appear to be about equally susceptible; 36 cases (12.8%) occurred in the colored inhabitants who make up 11.3% of the total population.

Although no age group is exempt, the tendency to affect predominantly children and young adults has been commented on by several writers on the subject, and is borne out by the observations in this epidemic. Table 2 shows the actual incidence by age groups; while Chart II shows the incidence rate per 100,000 in the same groups. Calculations are based on the 1930 census figures.

The cases were well distributed over the city, showing no predilection for the rich or poor, sanitary or insanitary, screened or unscreened houses. The "basin" is the older portion of Cincin-

nati, and is comprised of Census Tracts 1 to 11, 14 to 17, and 91. It lies along and near the Ohio River bank, and is the area where poverty and congestion are most prevalent and the screening of houses is at a minimum. This area contains 28% of the city's population and accounted for 29.4% of the cases of epidemic pleurodynia reported.

TABLE 2.—REPORTED CASES BY AGE GROUPS.

Age.	Cases.	Age.	Cases.
Under 5 yrs.	73	35 to 44 yrs.	18
5 to 9 yrs.	55	45 to 54 yrs.	5
10 to 14 yrs.	33	55 to 64 yrs.	3
15 to 19 yrs.	31	65 to 74 yrs.	0
20 to 24 yrs.	17	75 yrs. and over	2
25 to 29 yrs.	29		
30 to 34 yrs.	16		282

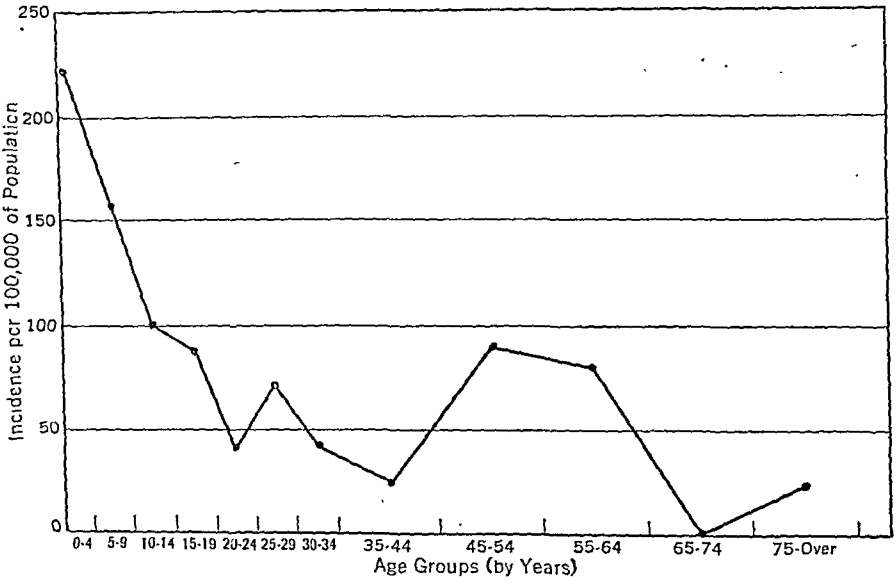


CHART II.—Incidence by age groups.

European authors[1] clearly recognized the communicability of the disease, although this fact has not been so promptly recognized in the United States, perhaps because of the negative view expressed by Dabney[2] in 1888. In this country the best demonstration of the communicability of the disease was made by Greene[7] who reported an epidemic occurring in a children's home in New York City; 11% of 1230 boys were affected, while the girls' department on the other side of the street had not a single case. The reason was that there was no intermingling of the boys and girls, although the climatic and mosquito surroundings were the same, as were also food, milk and water supplies.

In the Cincinnati epidemic 24 groups of contact cases were

noted. Of the 244 localities from which cases were reported 24 (9.8%) had more than 1 case. Not enough data are present for an exact expression of the communicability index.

No exact observations of the incubation time were made, but contemplation of the epidemic as a whole, and of groups of cases confirms the generally accepted view that the incubation period is short, in the neighborhood of a week.

Clinical Aspects. The diagnosis of epidemic pleurodynia is made almost entirely on a clinical basis, and with practically no help from the laboratory. Because of the unusual interest which the disease aroused in Cincinnati the attending physicians appended a few clinical notes to their reports in 86 instances. Such data are valuable from the positive side because they tend to present features which impressed the attending physicians, but have no significance from the negative side.

Of 77 cases in which single temperature readings were given, 45 (58.4%) lay between 101° F. and 103° F. The upper extreme was 104.6° F., and 4 normal readings were reported. The pulse rate was elevated approximately in proportion to the temperature, and in no case was it reported as slower than normal. Chills were mentioned 7 times, chilly feelings once, general malaise twice, headache 23 times. Recovery was usually complete in 4 to 5 days, often less, and seldom longer. The characteristic feature of the disease is the sudden onset of severe pain in the general region of the line of diaphragmatic attachment to the thoracic wall. It is intensified during respiration. Usually it is unilateral and predominantly on the thoracic side of the diaphragm, but not infrequently the abdominal features are striking enough to effect the simulation of an acute condition requiring surgical intervention. The pain tends to come in paroxysms, and may shift from one side of the thorax to the other. Frequently, there is tenderness of the chest wall along the line of diaphragmatic attachment. At the end of 12 hours considerable improvement is usually shown. This may signify the termination of the disease, but generally a relapse occurs on the third or fourth day almost as severe as the onset. From then on recovery is usually speedy. No complications, no fatalities, and no prolonged convalescences were observed. One case was reported in which a second attack occurred 20 days after the initial onset; whether this is to be regarded as a relapse or reinfection is a difficult distinction to make.

Physical signs are not very striking. Rapid shallow respiration because of pain is characteristic. The skin is hot because of fever. Friction rubs are infrequent; only two were mentioned in reports. This agrees with the experience of American authors who have recorded none, or a low incidence; it differs somewhat from the experience of the English authors, Williamson,[13] Lloyd[14] and Atlee, Amsler and Beaumont[15] who found friction rubs in over half

of their cases. Possibly the fact that most of the Cincinnati cases were studied in the home prevented the detection of transient friction rubs which might have been disclosed during more close observation in a hospital. One of the two friction rubs reported lasted only for a short time. The other persisted for a week after subsidence of the acute symptoms. This occasionally prolonged persistence of the rub has been commented on by Williamson.[13]

In only 9 cases were blood counts reported. Most of them were within normal limits. Two leukocyte counts were above 10,000. One of them subsequently fell to 3000, the only leukopenia in the group. Such a cycle, if common, would explain the contradictory reports in which some authors have described a leukocytosis and others a leukopenia. No plasmodia were found in any blood smears.

Differential Diagnosis. A few cases are suggestive of coronary thrombosis because of pain referred to the substernal region. Early pneumonia, pericarditis, and diaphragmatic pleurisy must also be considered. The chief danger arises when there is enough abdominal pain to suggest a surgical condition. Knowledge of the disease is the best safeguard against unnecessary operation. Usually the picture is characteristic enough to make the distinction easy, but at times it is very difficult. One very capable local surgeon informed us that he had removed three normal appendices in patients whose subsequent course showed them to have been afflicted with epidemic pleurodynia. At the time of the third operation he knew of the epidemic, but the picture of appendicitis was so closely simulated that he performed the operation. He observed that the appendix was normal, but the entire peritoneum had a somewhat violaceous tint.

Therapy. Therapy consists in relief of the severe pain and assurance that recovery will be early and complete. Occasionally, large doses of morphin do not completely control the pain.

Etiology and Mode of Transmission. The cause of the disease remains unknown. Attempts made in this epidemic failed to confirm the plasmodium theory of Small.[16] From observation of cases the spread seems to be through direct contact.

Pathologic Anatomy. There were no postmortem studies in this benign disease. Doctor Welborn's[17] study of a biopsied intercostal muscle was negative.

Immunity. In an epidemic involving only one season nothing can be said concerning permanent immunity.

Case Reports in one family. This family group illustrates the characteristic symptoms of typical and mild cases and suggests an abortive case. The relative immunity of adults in indicated, also the communicability of the disease. This white family is a rather healthy one, perhaps slightly below the comfort level financially, but well above the subsistence level.

CASE 1.—Harry H., aged 8 (typical case), was admitted to the Cincinnati Children's Hospital July 16, 1935. On July 14, 1935, he complained of pain in his stomach and had a temperature of 103° F. On the second day

he was symptom free and temperature was normal. At 4.00 P.M. on the third day he complained of pain in the left side of his chest and in his abdomen. His temperature rose to 103° F. General malaise, headache, and some nausea were present, but no vomiting. Physical examination showed grunting respiration, muscle spasm all over the abdomen, and tenderness localized to the epigastrium. Recovery was uneventful after the third day of illness.

CASE 2.—Ruth H., aged 6 (typical case), had her onset and was admitted to the same hospital on July 19, 1935. The hospital record reads: "This 6-year-old white female took sick this A.M.—pain in right flank. This was most complained of on inspiration. Child has not vomited, but fever has been complained of since onset of pains. Temperature 102° F. at present." General physical examination was negative except for fever; on July 20, 1935, temperature was normal; on the evening of July 21, 1935, temperature was up to 102.4° F. Recovery thereafter was rapid.

CASE 3.—John H., aged 10 (mild case), on the afternoon of July 20, 1935, on arrival at a picture theater, was suddenly stricken with such severe pain low in the left side of the chest and in the epigastrium that he fell to the sidewalk. Companions helped him home, and his symptoms cleared up in about 24 hours. No physician was consulted during this illness.

CASE 4.—Carl H., Jr., aged 14 (mild case), on the evening of July 27, 1935, went to the office of a district physician of the Cincinnati Health Department because of a slight discomfort low in the right side of his chest. The district physician said—"Carl if you were sicker I should say that you had the 'Devil's Grip' that the newspapers are so full of now." Carl H., Jr., then gave the information that other members of his family had been stricken with typical severe manifestations of the disease. His temperature and physical findings were normal. The symptoms were not severe at any time, and his recovery was rapid.

CASE 5.—Stephen H., aged 4 (possible abortive case), on July 29, 1935, had a temperature of 102° F., poor appetite and some malaise but no pain. By the next day he had recovered completely.

The parents, Carl H., Sr., aged 47 and Catherine H., aged 36, remained well during the epidemic, as did 2 other children, William, aged 6, and Barbara, aged 14, who were away from home.

Conclusions and Summary. 1. Epidemic myalgia or pleurodynia is an acute communicable disease characterized by severe pain in the region of the diaphragmatic attachment to the thoracic wall.

2. During the summer of 1935 an epidemic of this disease occurred in Cincinnati, Ohio, and 282 cases were reported to the Health Department.

3. Children are more susceptible than adults.

4. White and colored, male and female, sanitary and unsanitary individuals are about equally susceptible.

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ROCKY MOUNTAIN SPOTTED FEVER IN PENNSYLVANIA.

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According to the United States Public Health Service records,[1] only 3 cases of Rocky Mountain spotted fever have been reported to it from Pennsylvania, in 1930, 1932 and 1934, from Franklin, Delaware and Chester Counties, respectively. A case observed at the University Hospital, during June, 1935, is presented here in order to emphasize the salient features of the disease, and to remind the physician that the condition is no longer a medical curiosity in this region of the United States. We believe that the incidence of the disease, perhaps in a milder form, is greater in this section than these reports would indicate, due possibly to the failure voluntarily to report the disease, or to faulty diagnosis.

The disease was recognized in the Bitter Root Valley in Montana as early as 1873, but the clinical picture was first described by Maxcy,[2] in 1899. Since its recognition, Rocky Mountain spotted fever is known to have recurred from year to year, with little variation in locality throughout states of the Rocky Mountain region. Rumreich *et al.*,[3] in 1931, reported the first recognized cases in the East, from Delaware, Maryland, Pennsylvania, Virginia, North Carolina, and the District of Columbia. Since this report a number of other workers[4] have noted the appearance of the disease in this section of the country. How long it has existed in this section, and how extensive has been its spread elsewhere, is uncertain. It is known, however, that the disease is widespread

among many wild rodents, and is transmitted to man by the bite of an infected tick. The virus was demonstrated in these vectors by Ricketts.[5] The Dermacentor variabilis ("wood tick" or "dog tick"), shown to be the predominant carrier in the East,[3] appears in March, becomes most prevalent from May to July, and is occasionally found as late as October. Since these infected ticks usually remain undetected until man contracts the disease, the epidemiological character and geographic distribution of the disorder is based primarily upon human case reports. At present, the data indicate a focal endemic distribution, but sufficient information is not yet available for accurate delineation of the infected localities.

Rocky Mountain spotted fever may be briefly defined as an acute, endemic, infectious but non-contagious disease, widespread among many wild rodents, and transmitted to man by infected ticks. It is characterized clinically by onset with chills; a continued fever terminating usually by rapid lysis after 2 or 3 weeks; headache, muscle and joint pains; a macular eruption which becomes petechial, appearing about the fifth day on the wrists, ankles and back, and then spreading over the entire surface of the body. Convalescence[6] may be protracted but is usually complete; the fever is occasionally followed by deafness, visual disturbances, slurring of speech and mental confusion for a few weeks. The mortality in the eastern United States is about 25%.[7] The pathologic findings[8] are referable to the vascular system, where endothelial proliferation is followed by thrombosis, occlusion and perivascular accumulation of large mononuclear cells, particularly in the skin, brain, spleen and lymph nodes.

Although the clinical course and the character of the exanthem leads one to suspect the disease, the diagnosis must be confirmed by laboratory studies. At some stage of the disease, usually by the end of the second week, the blood contains sufficient specific agglutinins for one or more strains of proteus X, as demonstrated by the Weil-Felix reaction. Davis[9] emphasizes the importance of a second test about the twentieth day, if the first specimen taken between the tenth and fifteenth days fails to show these agglutinins. It is desirable to test the serum against proteus X–2 as well as X–19, as the former may be positive even when the latter is negative.

The Weil-Felix reaction is also positive in typhus fever. Rocky Mountain spotted fever, a tick-borne infection, occurs usually in the late spring and summer months. The rash is first noted on the wrists and ankles, with rapid extension over the trunk, face and extremities, including the soles and palms. Typhus fever, on the other hand, a flea- and louse-borne infection, is most commonly seen in the fall and winter months. The rash makes its first appearance on the body, and unless the case is quite severe will not spread to the face and extremities. If necessary, guinea-pig inoculation

and cross-agglutination tests are available through the Public Health Service to establish the diagnosis.

Since the disease is self-limited, and specific therapy unknown, symptomatic treatment and supportive measures must be relied upon.

Case Report. A. T., a white woman, aged 43, was admitted to the private service of Dr. Alfred Stengel, on June 16, 1935. Except for a chronic arthritis of 10 years' duration, she was well until June 9, at which

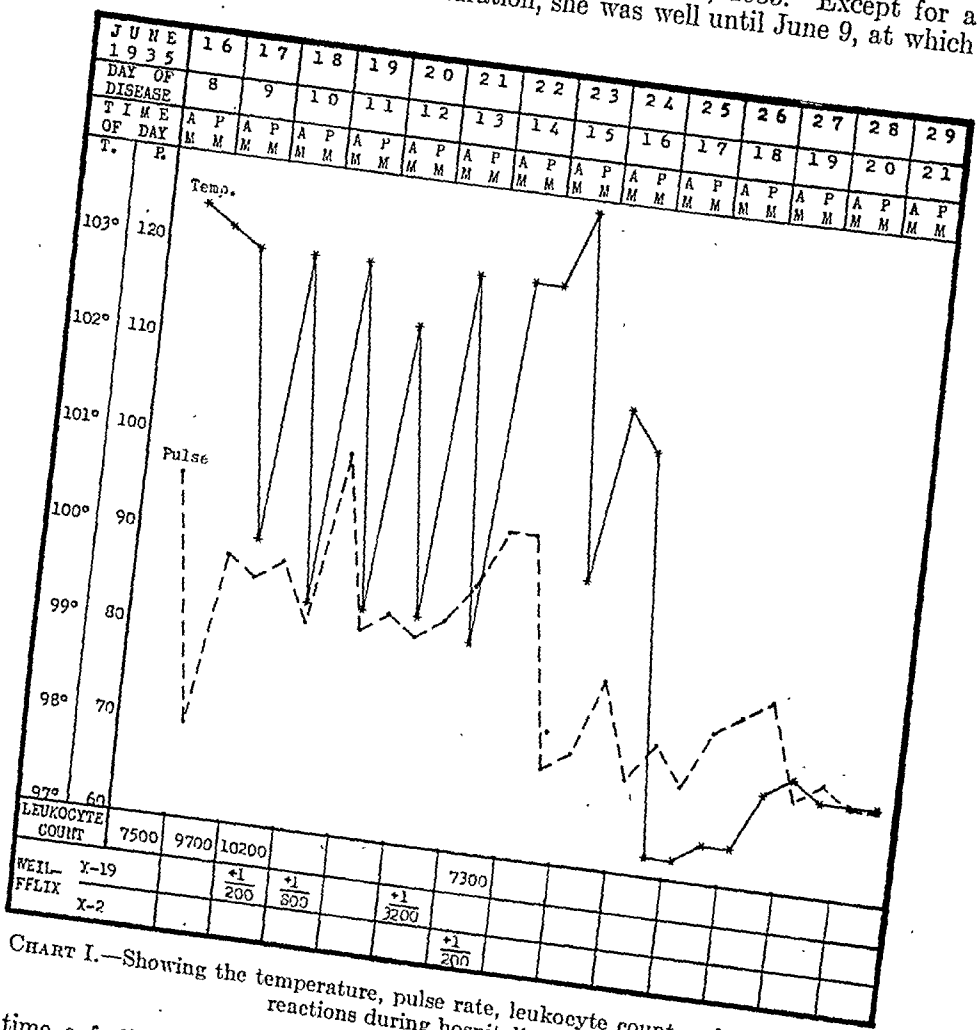


CHART I.—Showing the temperature, pulse rate, leukocyte count and agglutination reactions during hospitalization.

time a feeling of general malaise and lassitude forced her to bed. The following morning she complained of pain in her back and stiffness of all her joints. That night she experienced a severe chill, followed by a sudden rise in temperature (103° F.), generalized headache, and multiple joint pains. On June 12, there appeared rose-red spots on her knees and ankles, and next day the buttocks, wrists, abdomen and back were likewise involved. The elevation in temperature (101° to 103° F.), the multiple joint pains, the progressive skin lesions, and the severe headache persisted until her admission to the hospital. The patient had not been out of the immediate vicinity of her suburban home in Delaware County for several

months. There was no evidence of rodent infestation and her home sanitation was above reproach. About 2 weeks prior to the onset of her illness, the patient removed several ticks from her dog, but denied having been bitten.

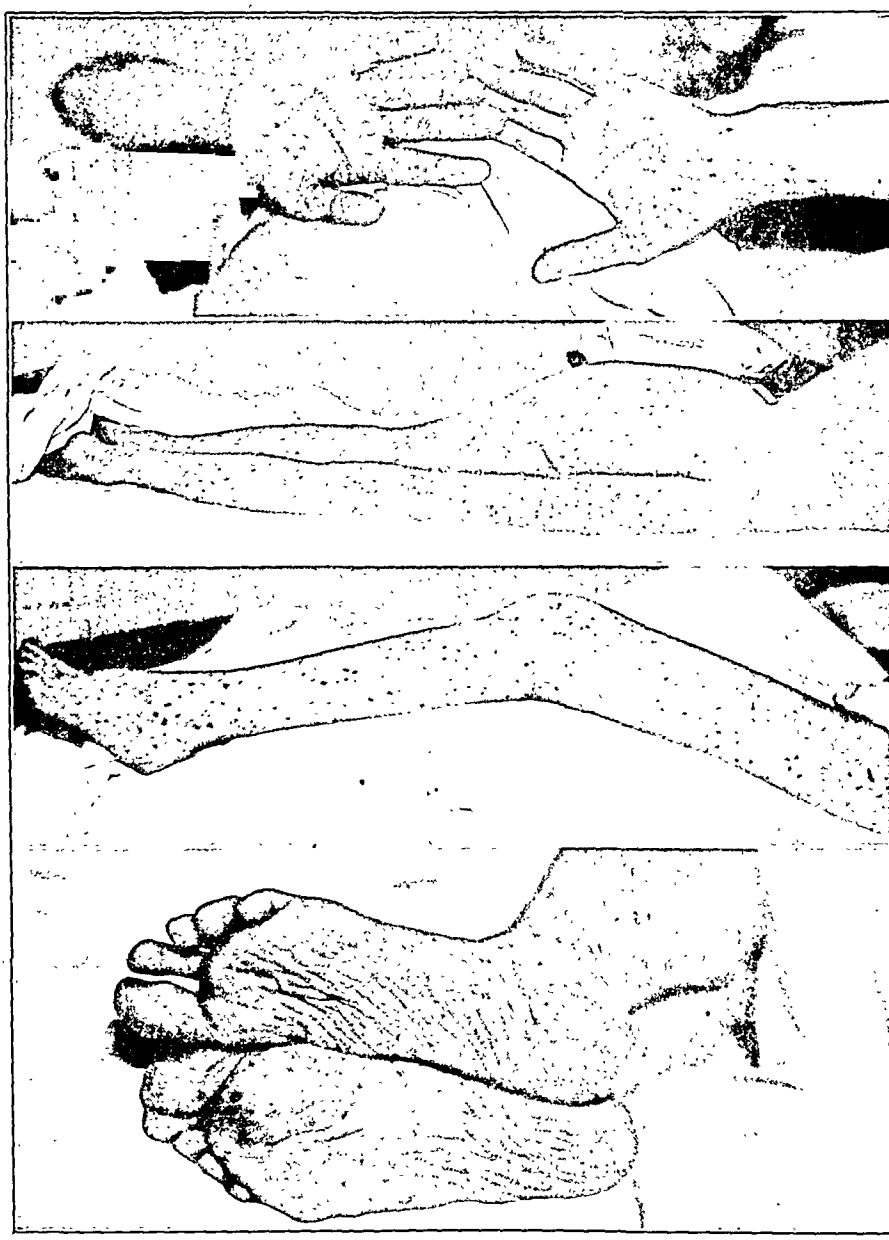


FIG. 1.—Photographs taken on the fourteenth day, showing the general distribution and petechial character of the eruption at this stage.

On physical examination, one found an acutely ill white woman, with temperature 103.2° F., pulse 96 and respirations 20. The entire skin

surface, excepting the face, was covered by a macular eruption, varying in color from red to almost purple, and measuring from 2 to 5 mm. in diameter. Some of the spots disappeared on pressure. All of the joints were painful, and there was generalized muscular tenderness. The tongue was heavily coated. Examination of the heart and lungs was negative except for the presence of a rather harsh systolic murmur heard over the apex of the heart. Laboratory studies showed 4,300,000 erythrocytes, 83% hemoglobin (Sahli), 7500 leukocytes, a normal differential picture and essentially normal urine.

After admission (Chart I) the patient continued to have an elevation of temperature, as well as joint and muscular pains. The chief complaint, however, was severe headache, intensified by ocular movement, and described as being worse than those suffered during an attack of typhoid fever (1910). At the height of the illness, she experienced terrifying dreams, chiefly during the daytime. The rash (Fig. 1) soon spread over the face and oropharynx. The first Weil-Felix reaction (X–19) on the tenth day was positive in a dilution of 1 to 200, and 3 days later in a dilution of 1 to 3200. On the fourteenth day, using X–2 strain, it was positive in a dilution of 1 to 200. The spleen was first palpable about the sixteenth day of the disease. On the seventeenth day the pyrexia subsided almost by crisis, and the rash began to fade. The patient was discharged on June 30, after an uneventful complete recovery.

Summary. 1. The case of a patient with Rocky Mountain spotted fever acquired in Delaware County, Pennsylvania, is presented.

2. Physicians should be aware of the presence of this disease in the eastern United States, especially in rural sections, during the spring and summer months.

3. The importance of reporting all cases as an aid in the epidemiologic study of the disease is stressed.

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ENCEPHALOMYELITIS FOLLOWING GERMAN MEASLES.

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It has been the general impression that German measles is a benign disease and that symptoms indicating involvement of the nervous system do not occur. Considering the frequency of the disease this impression is understandable. However, there is an increasing number of cases being recorded in the literature with very severe neurologic symptoms. We have seen 4 such cases in the past few months in Massachusetts, where there has been an epidemic of German measles. It is the purpose of this article to report the findings in 4 cases of German measles in which the central nervous system was involved, and to review the literature on this subject.

Case Reports. Case 1.—A white male, aged 5, on May 10, 1935, had a rash on his face and neck and a few swollen glands in his neck. He was not sick and went to school but was sent home on account of the rash. The family physician was called and a diagnosis of German measles was made. He advised the mother to keep the boy in the house for a few days. On May 13, while playing, he suddenly had a convulsion. The convulsive movements, which started on the right side and spread to the left side, lasted about 2 to 3 minutes. The patient was then unconscious for approximately 45 minutes. He had another convulsion on the night of May 14, and 2 more on the night of May 15.

On examination, on the morning of May 16, at this hospital, the patient was semistuporous. The temperature was 100° F. The head and eyes were deviated to the left. The pupils reacted normally to light and the optic fundi were normal. The right face, arm and leg were paralyzed. Visual fields could not be accurately tested, but the patient would not pay any attention to a light or other objects when presented in the right visual field, whereas he followed them readily in the left visual field. Psychomotor tests were unreliable. Spontaneous speech was absent, but he responded slowly to question. A few mistakes were made in naming objects placed before his eyes. Cutaneous sensation was apparently unimpaired. The knee jerks were absent, but the ankle jerks were present. The abdominal and cremasteric reflexes were absent on the right, but present on the left. The left plantar response was flexor in type and the right was questionably extensor in type.

Laboratory Data. The red blood count was 4,000,000; hemoglobin, 80%; white blood count, 7000. The urine was normal. Lumbar punctures performed on May 14 by Dr. Gorman showed that the [illegible] pressure was normal. The fluid was clear, containe[illegible]

per c.mm. and the globulin test was positive. On May 15, the cerebrospinal fluid was under a pressure of 80 mm. of water. The fluid was clear and contained 16 lymphocytes per c.mm. The protein content was 37 mg., sugar, 50 mg., and chlorid, 646 mg. per 100 cc. The colloidal-gold curve was 0121100000, and the Wassermann reaction was negative.

Course. The patient improved rapidly and on the morning of May 17 was bright and alert. The conjugate deviation of the head and eyes had disappeared. Examination of the visual fields was normal and no disturbance of speech was detectable. The paralysis of the right side was improving, but a few clonic movements of right face and arm occurred at intervals throughout the day. Within the next few days the weakness of the right side rapidly disappeared. The knee jerks and the right abdominal and cremasteric reflexes returned. With disappearance of the paralysis a slight intention tremor developed in the right arm, which persisted for a few days. After 10 days the patient was allowed out of bed and played with toys and colored crayons without any evidence of weakness, tremor or awkwardness of the right arm or leg. He was kept in the hospital a few days longer because his sister had just developed German measles. Examination of the spinal fluid before discharge gave normal results. The fluid contained 2 cells, the protein content was 27 mg., sugar 60 mg., chlorid 720, and the colloidal-gold reaction negative.

CASE 2.—(Dr. Putnam's Case.) A white housewife, aged 33, on May 24, 1935, became ill with a rash, swelling of the postcervical glands, vomiting and slight fever, which was diagnosed as German measles by her physician. She was sick for only 1 day. On May 27, 3 days after the outbreak of the rash, there was a return of the fever and vomiting accompanied by severe headache, dizziness and vomiting. The following day the speech became slurred. Examination at that time showed nystagmus and absent abdominal reflexes. On May 30, she complained of blurring of vision. She became disoriented and incoördination of the muscles was noted. On May 31, patient was in a curious uncoöperative state, usually sulky, but occasionally facetious. She was imperfectly oriented as to time, place and person and her memory was impaired. The nystagmus was still present and there was a slight weakness of the left side of the face. Movements of the arms were slightly incoördinated. The deep reflexes were normal, but the abdominal reflexes could not be obtained. Babinski's toe sign was present on the left side. There was no stiffness of the neck or Kernig's sign.

Laboratory Data. The red blood cell count was 5,000,000 and the white blood count 11,000 per c.mm. The cerebrospinal fluid removed by lumbar puncture on May 31 was under a pressure of 80 mm. of water. The fluid was clear and contained 5 lymphocytes per c.mm. The protein content was 82 mg.; the sugar, 73 mg. per 100 cc., and the colloidal-gold curve, 1123221100.

Course. The patient improved rapidly and was free of all symptoms within a few days. On examination 2 weeks later she was clear mentally, and the neurologic examination was negative except for absent abdominal reflexes and a questionably abnormal plantar response on the left side.

CASE 3.—(Dr. Horrax' Case.) A white boy, aged 14, on May 14, 1935, developed a rash and swollen glands in the neck, which was diagnosed as German measles by the local physician. Two of his siblings were also sick at the same time with German measles. He remained in bed for 2 days and the rash disappeared. On May 20, 6 days after the onset of the rash, he began to complain of headaches and on the next day, after vomiting several times, lapsed into coma from which he recovered after a few minutes. On May 22, he had another vomiting spell and became unconscious for 2 hours. On May 23, he again became unconscious, with labored respira-

tions, and was brought to the New England Deaconess Hospital. On the way to the hospital he recovered consciousness and twitching movements of the head, left arm and left leg occurred. Immediately on entry to hospital he again became comatose, the respirations depressed and he appeared in a critical condition.

Laboratory Data. A lumbar puncture was immediately performed. The pressure was 400 mm. of water. The fluid was clear and contained 45 white cells per c.mm. The protein content was 60 mg.; sugar, 60 mg.; chlorid, 714 mg., and the colloidal-gold and Wassermann reactions were negative. There was immediate improvement in the patient's respirations, the cyanosis disappeared and convulsions did not recur.

Course. He continued to improve and within 24 hours was conscious and rational and remained so. Neurologic examination was negative except for a slight right facial weakness and inequality of the pupils. He remained in the hospital for 10 days and was discharged without any symptoms or abnormal signs.

CASE 4.—An Italian female, aged 9, was admitted to this hospital, July 10, 1935, in a semicomatose condition. The mother stated that the child had been perfectly well until July 6, when a rash appeared on the arm, which rapidly spread to involve neck, face and chest, accompanied by slight fever. The child did not feel ill, but was kept in the house for 2 days, by which time the rash had disappeared. On the morning of July 10, while playing in the yard, she suddenly fell to the ground unconscious. She arose after a few seconds, ran confusedly around the yard and began to beat her head against a stone wall. She was carried to her home in a rigid state, cyanotic and frothing at the mouth. The family physician was called and the patient was given a hypodermic injection, after which she became quiet. In the afternoon the patient awoke and became maniacal, thrashing about in the bed, screaming loudly and would not respond to questions or commands. She was then brought to the hospital.

Examination at that time showed in addition to the maniacal behavior, stiffness of the neck, Kernig's signs and bilateral Babinski's sign. The knee and ankle jerks could not be obtained and the abdominal reflexes were absent. The temperature was 103° F., pulse 130 and blood pressure 90/60.

Laboratory Data. The red blood count and hemoglobin content of the blood were normal. The white blood count was 15,000. The urine was normal. The cerebrospinal fluid removed at cistern puncture was under a pressure of 80 mm. of water, and contained 30 cells per c.mm., 75% of which were lymphocytes. The protein content was 79 mg.; sugar, 82 mg.; chlorid, 655 mg. per 100 cc., and the colloidal-gold curve, 0012321000. The blood and cerebrospinal fluid Wassermann reactions were negative.

Course. She became more confused and restless and refused to take fluids by mouth. The temperature rose to 105° F. about 8 hours after entry. Large doses of sedatives were given to quiet the patient and fluids were forced by catheter introduced into the esophagus through the nose. The child remained delirious for about 48 hours, gradually improving, and on July 13, the third day after admission, she was able to sit up in bed and talk rationally. The stiffness of the neck was still present, but the reflexes had all become normal. Ten days later the patient was discharged from the hospital with no residua.

We have been able to find 7 cases described in the literature.[1] These cases will be discussed in connection with our own. In addition to these 7, several other cases are mentioned. Benard[1a] reported that he has seen 12 cases of German measles with meningeal symptoms in which the cerebrospinal fluid contained excess cells.

He also quotes Sevestre as reporting the case of a young woman with delirium during an attack of German measles, Alliot as mentioning stiffness of the neck and conjugate deviation in 1 case, and Labougle as reporting the case of a soldier with fever, violent headaches, semicoma, and athetoid movements, with recovery. Siegl[1d] states that Freud and Rie cite several cases of hemiplegia after German measles in their monograph on infantile hemiplegia. These cases are not included in the discussion because the original reports were either inadequate or were not available to us.

Discussion. The signs and symptoms in the cases of encephalomyelitis following German measles (rubella) recorded in the literature and in those examined by us are the same as those described by Ford[2] in cases of measles (morbilli). In general, the cases may be divided into two groups according to the clinical symptoms indicating the portion of the central nervous system most severely involved: (1) Cerebral; (2) spinal cord, or brain stem. Meningeal symptoms, such as headache, stiffness of the neck and Kernig's sign may be present in either group or may occur as the only indication of involvement of the nervous system. The cases with cerebral involvement may show mental confusion, delirium, stupor, coma, convulsions, hemiplegia, or other focal signs. Those with spinal cord or brain-stem involvement show paraplegia, urinary retention, pyramidal tract signs, absent reflexes, diplopia, or cranial nerve palsies.

Table 1 gives a summary of the 7 cases reported in the literature and our 4 cases. These cases are analyzed more in detail below.

TABLE 1.—SUMMARY OF THE SYMPTOMS AND SIGNS IN 11 CASES OF ENCEPHALOMYELITIS FOLLOWING GERMAN MEASLES.

Author.	Age.	Sex.	Days after onset of rash.	Headache.	Convulsions.	Stiff neck.	Neurologic signs.	Result.
Benard	..	..	4	0	0	0	Paraplegia; later bulbar paralysis	Died.
Debré	7	M	2	0	++	0	Coma; conjugate deviation to left	Recov.
Debré	8	M	2	+	++	0	Coma; mental symptoms	Recov.
Brock	23	F	3	++	0	+	Diplopia; urinary retention; Babinski	Recov.
Siegl	9	F	4	++	+	0	Mental confusion; bilateral Babinski	Recov.
Gennes	..	..	5	++	0	+	Mental confusion; urinary retention	Recov.
Skinner	10	M	3	0	+	0	Mental confusion; absent reflexes; Babinski	Recov.
Authors: Case 1	5	M	3	0	++	+	Conj. dev. to left; right hemiplegia and hemianopsia; absent K. J.; cerebellar signs	Recov.
2	33	F	3	+	0	0	Mental confusion; nystagmus; left Babinski	Recov.
3	14	M	6	+	+	0	Coma; muscle twitchings	Recov.
4	9	F	4	0	+	+	Mental confusion; delirium; absent reflexes; bilateral Babinski	Recov.

Age and Sex. The age varied between 5 and 33 years, with the great majority under 15. They are about equally divided between the 2 sexes.

Time of Onset of Involvement of the Central Nervous System. The interval between the appearance of the rash and the onset of neurologic symptoms in the 11 cases varied between 2 and 6 days, with an average of 4 days.

Vital Signs. The temperature is usually normal or only slightly increased with the onset of the involvement of the nervous system, but rarely it may be markedly elevated (103° to 105° F.), as in our Case 4. The respirations are usually not affected, but they may be markedly depressed, as in our Case 3.

Neurologic Signs and Symptoms. Headache was a presenting symptom in 6 of the 11 cases. Stiffness of the neck, or Kernig's sign, was found in 4 cases; attacks of unconsciousness with convulsive movements in 7 cases, mental confusion in 6, conjugate deviation of the head and eyes in 2, diplopia in 1, nystagmus in 1, hemiplegia and hemianopsia in 1, urinary retention in 2, paraplegia in 1, absent deep reflexes in 3, Babinski's toe sign in 5, cerebellar signs in 1 case and bulbar paralysis in 1.

TABLE 2.—THE CEREBROSPINAL FLUID FINDINGS IN 11 CASES OF ENCEPHALOMYELITIS FOLLOWING GERMAN MEASLES.

Author.	Cerebrospinal fluid findings.				
	Pressure, mm. of water.	Cells, per c.mm.	Protein, mg./100 cc.	Sugar, mg./100 cc.	Colloidal gold.
Benard		*			
Debré:					
Case 1	...	23	45		
Case 2	...	400			
Brock	...	296	70		
Siegl	...	33			
Gennes	...	90	40	70	
Skinner	...	13			
Authors:					
Case 1	85	50	35	50	0121100000
Case 2	80	5	82	73	1123221100
Case 3	400	45	60	60	0000000000
Case 4	60	30	79	82	0012321000

* Reported as increased. Number not given.

Cerebrospinal Fluid. The cerebrospinal fluid findings are summarized in Table 2. They are similar to those reported by Ford[2] in cases of measles encephalitis. The pressure is usually normal. Rarely it may be moderately or markedly increased (400 mm. in our Case 3). The cell count is increased, usually varying between 10 and 200 per c.mm. Rarely only a few cells are present or there may be several hundred cells per c.mm. (400 per c.mm. in Debre's Case 2). Lymphocytes are the predominating cell type, but a few neutrophils are usually present. The protein content is moderately increased. The sugar content is normal. The chlorid content is

normal or slightly decreased. The colloidal-gold reaction is normal or shows a midzone curve. The fluids are sterile.

Pathology. The pathology of encephalomyelitis following German measles has never been carefully studied. A necropsy was performed in Benard's case, but the histologic changes were not described. He merely states that there was an acute myelitis, disseminated over the entire cord. There is no reason to believe that the lesion in these cases is any different from that of measles encephalomyelitis as described by Greenfield,[3] and by Ferraro and Scheffer.[4] The etiology of the nervous involvement is not known. Similar pathologic changes have been reported in cases of encephalomyelitis following variola, vaccinia and other exanthemata. It has been suggested that possibly a filtrable virus may be the etiologic factor, but it is our feeling that the lesions can best be explained on the basis of vascular changes as suggested by Putnam.[5]

Frequency. We are unable to give any estimate as to the frequency of involvement of the central nervous system in cases of German measles. We are sure that the few cases reported in the literature do not represent a fair estimate of its occurrence, as most neurologists with a wide experience have encountered 1 or more cases. It is probable, however, that the frequency is less than the 0.4% as given by Ford for measles.[2]

Diagnosis. When the typical history of the onset of mental or neurologic symptoms 2 to 6 days after the rash is obtained there is usually no difficulty in the diagnosis. The cerebrospinal fluid findings serve to confirm the diagnosis. There has been doubt, however, in the minds of some clinicians concerning the validity of the diagnosis of German measles (rubella) in the cases that later develop encephalomyelitis, and they properly question whether these were not mild cases of measles (morbilli). The diagnosis in both of these exanthemata is a clinical one. Therefore we do not see the justification for making a retrospective change in the diagnosis in a typical case of German measles when neurologic symptoms develop.

Prognosis. There has not been a sufficient number of cases recorded in the literature to draw any definite conclusions in regard to the mortality or as to the ultimate outcome in the cases that live. Only 1 of the 11 cases shown in Table 1 died, which gives a mortality of 9%. This is approximately equal to that (10%) found by Ford[2] in measles encephalitis. Ford reported sequelæ in 65% of the cases of measles encephalitis divided as follows: residual weakness, 30%; ataxia, 12%; mentality defects or personality changes, 17%; epilepsy, 5%. While none of the cases of encephalomyelitis following German measles has shown any paralysis or ataxia, most of the cases recorded in the literature, as well as those observed by us, have not been followed long enough to determine whether mental defects, personality changes or epilepsy

may result. It is perhaps noteworthy that the disabling Parkinsonian syndrome, which is so frequently a sequel of epidemic encephalitis, has never been recorded in the post-measles or post-German measles encephalitis.

Summary. The clinical history and findings in 4 cases of encephalomyelitis following German measles (rubella) are reported. The literature on this subject is reviewed and these cases are compared to those that occur after measles (morbilli).

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OBSERVATIONS ON THE EFFECT OF MALARIA ON THE WASSERMANN REACTION.

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The occasion not infrequently arises in sections where malarial fever is prevalent when it becomes necessary to interpret a positive Wassermann reaction of the blood serum taken during the course of such an infection. The question as to whether or not malarial fever does cause such changes in the blood serum as may give false-positive serologic reactions has been much disputed, and has been the subject of many reports. Because of the inconclusiveness of the available literature and because of the importance of this question in the subsequent management of the patient, we have thought it worthwhile to review the experience of the Roper Hospital,

situated in a locality where both malaria and syphilis are common, in an attempt to throw further light on this disputed point.

While an extensive literature has accumulated regarding the influence of malarial fever on the Wassermann reaction, most reports deal with cases studied some years ago, in which only complement-fixation tests were performed, and before many of the newer serologic tests for syphilis had been developed. According to Lloyd and Mitra,[1] the opinion that malaria is responsible for non-specific positive reactions in certain cases originated largely from the address given to the British Medical Association by Wassermann in 1910. These authors have prepared an excellent summary of the more complete reports up to the time of their writing, from which they conclude that little reliance may be placed on many of the earlier observations because of faulty technique in the performance of the serologic tests and because of the inadequacy of precautions taken to exclude the possibility of syphilis. In their own cases, 85 in number, positive reactions were found in 14%, which they state falls easily within the expected syphilis rate of their hospital population in Calcutta. They conclude, therefore, that there is no evidence that malaria causes positive serologic reactions when modern techniques are carried out. A similar conclusion is reached by Thomson and Mills,[2] Iyengar,[3] Levy,[4] Johnson,[5] and Chambers.[6]

A diametrically opposite view is taken by other observers, many of whom maintain that at times malaria is a cause of false-positive serologic reactions. Craig[7] made this statement in a paper upon the complement-fixation test published in 1910, and repeated the opinion again in 1921.[8] St. John,[9] likewise, found non-specific reactions in 4.9% of a total of 101 cases of acute malaria. More recently, in the studies made for the evaluation of the serodiagnostic tests for syphilis in this country,[10] of 36 presumably non-syphilitic patients with malaria, positive serologic reactions were found in from 8.6 to 20.6%.

Confusion in regard to this question has arisen largely from two factors. In the first place, the results have been obtained over a period of years, using widely different modifications of the original complement-fixation technique, all of these being designated as the Wassermann reaction. It is of particular significance that most of the false-positive cases were reported in the early days of the complement-fixation test, and that with the modern advances in technique and in standardization, fewer non-specific positive reactions are being reported now than formerly. Secondly, because a definite history of primary infection is so often lacking, and because the physical signs of the latent stage of syphilis so often escape notice, the correct interpretation of a positive serologic reaction, obtained in the presence of another infection, is beset with difficulty. While it is surely safer to place more reliance on serologic than on

other evidence of syphilis, some observers seem to have erred in accepting the former with too much finality, and they are liable to almost as much criticism as those who dismiss the possibility of syphilis when a suggestive history or physical findings are not obtained. The middle road is indeed difficult to reach.

Material and Results. The present study is based on the case records of 262 patients, representing all of the cases of malarial fever admitted to the Roper Hospital during the years 1930 to 1934, inclusive, in which parasites were found in the blood smear and the serologic tests for syphilis were performed. Those cases were excluded in which the tentative diagnosis of malaria was made, based on clinical findings but unsupported by positive identification of parasites, as well as all cases in which serologic tests were not carried out. Throughout this period, the Kolmer modification (qualitative) of the complement-fixation test was used; in addition, during 1930 and 1931, the standard Kahn flocculation test was done routinely, while from 1932 to 1934, the Kline diagnostic test was carried out. The series of 262 patients includes 134 whites and 128 negroes. *P. vivax* was found in the blood smear in 159 instances, *P. falciparum* in 75, both types of parasites in 15, while in 13 cases positive differentiation between the two types was not made. In this group of patients, negative serologic tests were found 192 times (107 white, 85 negro), and positive results of varying degrees of strength in 70 cases (27 white, 43 negro).

In attempting to interpret the positive serologic findings in the group of 70 cases in which they occurred, a study was made of all relevant data that could be obtained: (1) A suggestive history of primary or secondary lesions of syphilis; (2) a history of previous specific treatment; (3) previous serologic tests; (4) subsequent serologic tests; (5) physical findings suggestive of syphilis, or findings compatible with that diagnosis, another explanation for which was not found. On the basis of these criteria, 23 cases were excluded as definitely syphilitic and 23 cases as probably syphilitic. In 9 cases adequate follow-up studies could not be made and these, therefore, were likewise excluded. Of the remaining cases, 15 in number, we believe 13 were definitely non-syphilitic and 2 possibly so in which the positive serologic tests were due to malaria; in none of these cases was there a history of any primary or secondary lesion, and in all physical examination disclosed none of the signs of a latent syphilitic infection. The essential findings in the first 12 cases of this false-positive group are noted in Table 1. None of these patients received antisyphilitic treatment, either before or during their attack of malaria, or afterwards in the interval between serologic tests.

One additional case seems worthy of more detailed consideration. The patient, a white man, aged 26, was admitted to the hospital on June 28, 1934, with a story of fever of 3 days' duration, and nausea and vomiting. Slight rigidity of the neck, noted early the

next morning, led to lumbar puncture. The findings in this and in the subsequent spinal fluid examinations, along with the results of the serologic tests on the blood serum, are noted in Table 2. The patient remained afebrile for several days after admission, but the fever returned, and on July 10 malarial organisms of the tertian type were found in the blood smear. Treatment with quinin was begun, the serologic tests on July 16 being done after 75 grains of the drug had been given. Neither during the patient's stay in the hospital nor at subsequent examinations were any physical or neurologic signs noted to substantiate a possible diagnosis of syphilitic involvement of the central nervous system.

TABLE 1.—PATIENTS WITH FALSE-POSITIVE WASSERMANN REACTIONS DUE TO MALARIA.

No.	Color.	Age, yrs.	Type of infection.	Therapy before serologic test, gr.	Temp. at time blood taken.	Serologic test.	Date.	Repeat serologic test.	Date.	Repeat serologic test.	Date, 1935.
1 . . .	W	19	T	Q 25 P ½	102	W 0 K++	11-6-32	W 0 K 0	11-16-33	W 0 K 0	1-19
2 . . .	W	27	T	Q 70	100.6	W++ K +	9-18-33	W 0 K 0	12-15-34		
3 . . .	W	14	T	None	99	W + K++	11-6-33	W 0 K 0	11-23-33	W 0 K 0	2-3
4	W	30	T	Q 75 A 12	99	W++++ K++++	11-13-33 11-16-33	W 0 K 0	8-29-34	W 0 K 0	1-19
5 . . .	C	25	T	Q 20	98.6	W++++ K 0	12-13-34	W 0 K 0	1-27-35		
6 . . .	W	34	T	Q 60	99	W++ K++	10-2-33	W 0 K 0	3-14-35	W 0 K 0	7-24
7 . . .	C	3	T	A 9	99.4	W+++ K+	9-6-34	W 0 K 0	1-27-35		
8 . . .	C	15	T	A 3	104	W 0 K++	7-23-34	W 0 K+	7-30-34	W 0 K 0	3-26
9 . . .	W	7	EA	A 12 P 1½	99	W++ K 0	11-13-33	W 0 K 0	1-24-35		
10 . . .	W	25	EA	Q 40	101	W+++ K 0	8-6-34	W 0 K 0	8-20-34	W 0 K 0	1-14
11 . . .	C	14	EA	None	101	W++++ K 0	8-30-34	W++ K 0	9-6-34	W 0 K 0	1-27
12 . . .	W	11	M	A 7½ P 5/6	100	W+++ K 0	11-13-34	W 0 K 0	11-16-34		

Abbreviations: T = Tertian; EA = Estivo-autumnal; M = Mixed; Q = quinin sulph.; A = Atebrin; P = Plasmochin; W = Kolmer test; K = Kline test.

TABLE 2.—CASE WITH FALSE-POSITIVE SPINAL FLUID WASSERMANN REACTION.

Date:	6-29.	7-2.	7-9.	7-16.	Nov.	Jan.
Spinal fluid serology .	W++++ K 0	..	W 0 K 0	W 0 K 0		
Spinal fluid cell count	4	..	..	5		
Blood serology . .	..	W 0 K 0	..	W++ K 0	W 0 K 0	W 0 K 0
Temperature . . .	Nor.	Nor.	100°	99°	Nor.	Nor.

W = Kolmer test. K = Kline test.

Discussion. From the evidence at hand, it would seem that in all of the above cases the positive serologic tests were non-specific. While historic methods are notoriously inadequate and while the physical signs of a latent syphilitic infection are often minimal and difficult to elicit, in the absence of both of these indications the diagnosis of syphilis cannot be sustained when the sole basis for the latter has been a weakly positive serologic test. And this is especially true when the serologic reaction becomes and remains negative without any specific treatment whatsoever. In the group of 13 false-positive cases, there was agreement between the Kolmer and Kline tests in 5 cases and complete disagreement in 8; of the latter, the Kline test remained negative in 6, the Kolmer test in 2. In the 3 cases of estivo-autumnal malaria and the case of mixed infection, the Kline test was negative. The temperature at the time the blood was taken for serologic tests seemed to have made no difference in the results, being under 100° F. in 7 cases, and over 100° F. in only 6. The kind and amount of treatment prior to the test was likewise inconsequential in the results obtained. In the group of 193 sero-negative cases, which may be used as controls, the temperature ranged from normal to 106° F., and the amount and kind of treatment before testing was also sufficiently varied as to serve as an adequate control for this possible factor.

Whether or not the positive spinal fluid complement-fixation test in Case 13 (Table 2) can be considered as a non-specific reaction due to malaria is debatable. This condition has not been previously reported, but it is not surprising in view of the fact that the occasion for lumbar puncture does not arise very frequently in patients with malaria. In this case, while the patient was undoubtedly infected with malaria at the time the test was performed, parasites were absent from the peripheral blood and there was no fever. The temperature did not begin to rise again until about 1 week later, after which time tertian organisms were definitely identified. However, no other possible explanation for this false-positive result can be advanced, and it is reported here as being possibly due to malaria. In 7 other cases in which spinal fluid examination was made, the results were negative in 5, and positive in 2 known syphilitic patients.

Statistical analysis shows that in the entire group of 262 patients, positive serologic tests were found in 20.1% of the white patients and 33% of the negro. The normal syphilis rate for this community was studied some years ago by Johnson,[11] whose reported that in 30,000 serologic tests, 15% were positive in white patients, 45% in negro. The discrepancy between these figures and the percentages found in the group of malarial cases probably lies in the fact that almost half of the negro patients in the malaria group were under 12 years, whereas in the general hospital population, children account for a much smaller percentage of admissions. If the adult negro patients are considered alone, 48.5% gave positive serologic

results, a figure close to the expected average. Excluding the definitely and possibly syphilitic patients, false-positive results were found in 6.3%.

Two additional cases remain for brief consideration. In the first, a white woman, aged 38, with estivo-autumnal malaria, strongly positive Kolmer and Kline tests were found and the patient was given a single injection of neoarsphenamin, 0.3 gm. Serologic tests repeated 1 month later showed the Kolmer reaction negative, the Kline test 2+. Subsequent tests, 1 and 2 months later, were negative by both methods. The temperature was elevated (101° F.) and parasites were present in the blood at the time the first tests were made. The second case was very similar, save that here the patient received 9 injections of neoarsphenamin, a total of 5.1 gm.; serologic tests became negative and had remained so $1\frac{1}{2}$ years later. Both of these cases illustrate the difficulty in the subsequent management of the patient when antisyphilitic treatment is begun without sufficient clinical justification. It is easily possible that the second patient noted above had syphilis as well as malaria, but it is unlikely in the first case that a single injection of neoarsphenamin would be sufficient to cause the serologic reaction to revert to negative, if the latter were due to syphilis. However, because these 2 patients received specific treatment for syphilis, we have not felt justified in including either in the group of false-positive reactions due to malaria.

We have in no way attempted to ascertain the cause for the appearance of these non-specific positive serologic reactions which occur during the course of malarial fever. The mere fact of increased temperature has been assumed to be the cause of such false-positive reactions by some authors,[12] who state that negative results are obtained after the temperature has become normal. Kolmer[13] has emphasized the fact that acute febrile diseases may render the blood serum temporarily more anticomplementary, making it necessary to guard against non-specific reactions, but obtained no positive results in 11 cases of malaria. However, in the group of 36 cases of malaria tested recently by this method,[10] 19.4% positive reactions were found. In our own cases, we have not found that the temperature made any difference in the specificity of the results obtained. The therapeutic agents used in the treatment of malaria have likewise been eliminated as possible etiologic factors. The presence of malarial parasites in the peripheral blood stream has also been cited as a cause;[12] we have not examined the blood with sufficient frequency to determine whether or not parasites were demonstrable on the days on which the tests in our cases were taken, but judging by the amount of treatment that some of the patients had had, it is unlikely that this factor could have been responsible for all. An individual idiosyncrasy of some nature is possible, but 2 of the patients in our false-positive group were observed in recurrent attacks of malaria 1 and 2 years following their original attack,

at which times the serologic tests remained negative. The most recent suggestion as to the cause for the occurrence of these non-specific reactions has been made by Fischer and Günsberger,[14] who claim that the positive serologic reaction is traceable to the presence of antibodies directed specifically against erythrocytic lipoids liberated by the action of the malarial parasites on the red blood cells. These authors describe an extract of beef heart, relatively poor in these lipoids, which generally does not react with serum from malarial patients or reacts only weakly, although it is an excellent antigen for the test for syphilis. They state that the Wassermann reaction carried out simultaneously with the erythrocytic reaction can distinguish Wassermann-positive malaria from syphilis.

Summary. Because of the controversial nature of the literature in regard to the influence of malarial fever on the Wassermann reaction, we have examined the case records of 262 patients with malaria. Excluding those cases in which there was any suggestion of the possibility of syphilitic infection, non-specific positive serologic results were found in 6.3%.

One case is reported in which the spinal fluid complement-fixation test was positive, most probably a non-specific reaction due to malarial infection.

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COLLAPSE THERAPY FOR TUBERCULOSIS IN THE SMALL SANATORIUM.

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When this sanatorium was opened, in 1931, the extensive use of collapse therapy was, with rare exceptions, restricted to large sanatoria and other tuberculosis centers. Being convinced that collapse therapy was as essential for good results in a small sanatorium as in a large one, we determined to give our patients the benefit of this therapy whenever indicated. The results of this program, from every point of view, have been so satisfactory that we feel that our experience should be reported briefly.

The Jackson County Sanatorium has a capacity of 58 adult patients. The medical staff consists of only one physician, who also conducts the out-patient department and administers the business affairs of the institution. He carries out all pneumothorax treatments. At a distance of 35 miles there is an experienced thoracic surgeon who is consultant of the sanatorium. He visits the sanatorium at frequent intervals for a medico-surgical consultation. He performs only the phrenic nerve operations at the institution; more extensive operative procedures are performed at his hospital where the patients may be under constant surgical supervision during their immediate postoperative convalescence.

The ensuing study covers the period from January 6, 1931, to September 1, 1934.

The National Tuberculosis Association has recently published average results based upon a survey[1] of all civilian sanatoria in the United States in 1931. It is well known that the percentage of use of collapse therapy in the country as a whole in 1931 was relatively low. Seventeen per cent of the patients in their report were discharged as arrested or apparently arrested,* 41% as quiescent or improved, 19% as unimproved and 23% as dead. One hundred and nine patients have been discharged from this sanatorium, where 48% have received collapse therapy, with the following results: 55% arrested or apparently arrested, 25.8% quiescent or improved, 0.9% unimproved and 18.3% dead.

The National Tuberculosis Association figures show that 49% of the patients were in the far-advanced stage of tuberculosis upon admission, 28% moderately advanced and 15% minimal. The corresponding figures for the Jackson County Sanatorium concerning 157 admissions are 59.2%, 28%, and 12.8%, respectively.

The contrast between the foregoing discharge results is even more

* The stage of the disease and the results are classified according to the criteria of the National Tuberculosis Association.

striking if the fact be accepted that the great majority of the patients who were unimproved, and a considerable proportion of those classified as improved and quiescent, will probably die. Nineteen per cent of the patients in the National Tuberculosis Association report were classified as improved upon discharge and an additional 23% were dead upon discharge, a total of 42%. Only 0.9% of our patients were unimproved upon discharge and 18.3% were dead, a total of 19.2%. The sum of the dead, unimproved, improved and quiescent in the National Tuberculosis Association report is 83%, and in our report only 45%. Only 17% of the National Tuberculosis Association patients had arrested tuberculosis, whereas 55% of ours had. Still further significance may be attached to the comparative results when it is revealed that 45% of those dying in our group were too ill to be considered for collapse therapy—this giving a death rate of but 10% among all patients considered upon admittance as having any possible opportunity of recovery. Incidentally, we have made no attempt to select favorable cases for admission; this is illustrated by the fact that 59.2% had far-advanced tuberculosis upon admission, whereas only 49% of the patients admitted to all civilian sanatoria in the United States in 1931 had far-advanced disease.

We have used collapse therapy on every patient for whom we felt that it was strongly indicated. In some of our minimal and moderately-advanced cases and in a few far-advanced cases we did not use collapse therapy because we felt that their chances of recovery without it were good and our limited financial resources at the time required that we should reduce expenditures to the minimum. Nevertheless, we believe that temporary phrenic paralysis or pneumothorax should be used even for those cases who may recover without collapse therapy, for the reason that these measures, when properly used, definitely increase the chances of recovery and hasten it.

Collapse therapy has been used upon entrance in only 5% of our minimal cases, in 50% of our moderately-advanced cases, and in 56.9% of our far-advanced cases: an average total of 48.4%. It is interesting that 36% of our far-advanced were admitted to the sanatorium in such poor condition that no collapse therapy could reasonably be considered.

During the $3\frac{3}{4}$ years, 109 of the 157 patients with the adult type of pulmonary tuberculosis who have been admitted to the sanatorium have been discharged. The 109 patients do not include 16 who left, against medical advice, less than 3 months after admission, or who entered the sanatorium within 3 months of the preparation of this report. These patients are excluded because they obviously are unsuitable to illustrate the effect of treatment.

The results upon discharge of the 109 patients in whom the results of a fair trial of treatment are known appear in Table 1.

TABLE 1.—RESULTS AT TIME OF DISCHARGE (109 PATIENTS).

Classification at admittance.	Arrested or apparently arrested.		Quiescent.		Improved.		Unimproved or worse.		Died.		Total.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
Minimal	14	93.3	0	0.0	1	6.7	0	0.0	0	0.0	15	100.0
Moderately advanced .	24	72.8	6	18.1	2	6.1	0	0.0	1	3.0	33	100.0
Far advanced	22	36.0	9	14.8	10	16.4	1	1.6	19	31.2	61	100.0
Total	60	55.0	15	13.8	13	12.0	1	0.9	20	18.3	109	100.0

Whitney and Myers[2] reviewed the results of nearly 7000 cases discharged from two state sanatoria, one in an eastern industrial state and one in a southern agricultural state. They report 39% of the far-advanced cases as having died by the end of the first year and 52% by the end of the second year. After excluding patients leaving against medical advice after hospitalization of more than 3 months, and excluding transfers to other institutions, we have been able to follow 70 patients who have been voluntarily discharged by us within from 3 years to 3 months and find 95.8% still well, with no deaths. The tuberculosis in 3 (4.2%) became reactivated; these 3 patients, who had not previously had collapse therapy, returned to the sanatorium and have had collapse therapy.

An additional analysis of the group of 70 patients followed after discharge revealed that in the minimal group 6.6% had a positive sputum on entrance, none had cavitation; in the moderately-advanced group 39.2% had positive sputum and 24.1% had cavitation; in the far-advanced group 92.2% had positive sputum and 74% had cavitation. Upon discharge none of these patients had either a positive sputum or a cavity.

In view of the fact that we have used collapse therapy for the patient whose prognosis was obviously poor without it, it would be futile to compare the results of those patients who received collapse therapy with those who received only the unaided sanatorium regimen.

It is interesting, however, to note the results that have occurred in 26 cases who left the sanatorium against medical advice at some time before their treatment was completed. Of this number, 7.6% are improved, while 92.4% are unimproved, worse or dead (28% dead). It is significant that 38% of the group that did badly reëntered the sanatorium for treatment and none has died; collapse therapy has been instituted in all cases.

Conclusion. A rather extensive use of collapse therapy, in connection with the sanatorium regimen, tremendously improves the

results of the unaided sanatorium regimen. It is hoped that this report may stimulate a greater interest in collapse therapy in small sanatoria, as well as in large ones.

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PUNCH-DRUNK.

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There is a clinical syndrome of frequent occurrence among boxers, to which they refer as "punch-drunk," "punchy," "goofy," "slap happy," "cutting paper dolls," or "slug nutty." Other terms might be applied, such as "traumatic dementia" or "traumatic encephalopathy," but they are not nearly so appropriate and descriptive as the epithet "punch-drunk." The above terms were always somewhat familiar to me, and with the development of a medical viewpoint, I wondered if there really existed a traumatic dementia, such as indicated by these names, or if they were misnomers charitably denoting a traumatic origin to an incidental mental abnormality. The impetus to investigate this question and, if possible, to add to the original description of this condition given by Martland,[1] in 1928, came with the necessity of preparing a thesis for graduation.

I determined to study "punch-drunk" in its natural habitat, the boxing world. Accordingly, I frequented training quarters, helped examine fighters, and made friends with all sorts of "pugs." I observed declining veterans of the ring, talked with their trainers, and drank beer with their managers. I interviewed sports writers, referees and boxing commission physicians. I sought out reputed "punch-drunks" and studied them to the fullest extent that their feeling of exuberant good health would permit of a medical examination. My knowledge of the subject, then, is based upon the information given me by laymen whose business is a keen study of boxers, and the incomplete observation, over a period of 2 years, of many cases of "punch-drunk."

The course of a typical case is somewhat as follows: A sturdy young man trains in a gymnasium as an amateur boxer in order that he may develop himself physically, and master the finer points of pugilism. He becomes a fairly tough opponent in the ring, but he tends to fight rather than box, and so receives some degree of

punishment in each of his 30 or 40 short amateur matches. Later, he becomes a professional, meets stiffer opposition, engages in longer fights; but he is young, strong, and is "making good money." After a period of approximately 4 years as a professional boxer, during which time he has engaged in about 30 to 60 bouts, he begins to "soften up." His tolerance to all head blows is reduced. After being struck on the jaw, he remains dazed for a longer period than formerly, and is more likely to be knocked out ("glass jaw"). After a blow to the head, his legs will be a little shaky, and feel numb. His timing begins to fail and the fighter is no longer as dangerous on offensive as he had been. His defensive, which had been steadily improving with each encounter, becomes also less effective, and the pugilist who previously had been adroit enough to go through a career unmarked now begins to develop a flat nose and cauliflower ears. Later his knees tend to give way after a head blow, and a slight dragging of the feet may be noticed, although often only as the contestant is walking to his corner at the end of a round. The fighter still boasts of feeling fine and capable, but now loses engagements which formerly he could have won with ease.

Meanwhile the boxer's manager and associates begin to notice changes in him. They find that he has developed deterioration in attention, concentration and memory. In the midst of a conversation he may go into a reverie, suddenly change the subject, or ask the same question several times. He is apt to become too sociable, and very voluble. Usually an impediment of speech will develop, and the eyes may become slightly glazed or have a staring expression ("glass eye"). In short, he may continuously simulate a person who is just a little drunk. When these symptoms have once appeared, they will not only persist, but may progress for a period of a year or so when they will usually become stationary. Thus punch-drunk is a self limited rather than a progressive encephalopathy.

In the severer cases, the voice may become thick, halting and guttural, as though there were something held in the mouth. The gait may become unsteady. In a few instances vision may begin to fail or some degree of deafness may appear. Headache, dizziness and tinnitus, which one might expect as symptoms, are often present for a few hours or days following a fight, but they rarely persist as a part of the syndrome. Mental and personality changes become more marked, and emotional instability becomes apparent. Involuntary habit movements of a boxing nature are common, and are frequently displayed, even years later, when the person is abstractly preoccupied or during periods of emotional stress. A punch-drunk, sitting as a spectator at a fight, may vigorously ape the blows of his friend in the ring, oblivious to the other people about him. Punch-drunks almost universally do not realize that there is anything abnormal about themselves or their conduct, and

will hotly resent, often with their fists, any application of this stigma to themselves.

The more intelligent boxers are alert to recognize even early manifestations, and from the beginning plan retirement from active competition in the ring when ominous signs and symptoms first appear. The incident which precipitated Gene Tunney's decision to retire occurred during training for the second Dempsey fight. Tunney writes, "I went into a clinch with my head down, something I never do. I plunged forward, and my partner's head came up and butted me over the left eye, cutting and dazing me badly. Then he stepped back and swung his right against my jaw with every bit of his power. It landed flush and stiffened me where I stood. Without going down or staggering I lost all consciousness of what I was doing, and instinctively proceeded to knock him out. Another sparring partner, Eddie Eagan, entered the ring; we boxed three rounds. I have no recollection of this, nor have I any recollection of anything that occurred until the next morning when I awakened, wondering who I was and what I was doing there." For the next 3 days, Tunney was dazed and disoriented. He continues, "From that incident was born my desire to quit the ring forever, the first opportunity that presented itself. But most of all I wanted to leave the game that had threatened my sanity before I met with an accident in a real fight with 6-ounce gloves that would permanently hurt my brain. The possibility of becoming punch-drunk haunted me for weeks."[4] But the majority of boxers do not have this insight. They will continue to fight until they become so ineffectual in the ring that the promoters refuse to book them for any further matches. Some fighters, usually from economic necessity, will then enlist as sparring partners and receive further punishment while assisting in the training of others.

The type of boxer is a large factor in the likelihood of punch-drunk developing. It is most often seen in the wide-open slugging type of fighter who is out to give as much as he can, and thus usually takes quite a lot in return. It is rarer in cleverer boxers except after an extraordinarily long period in the ring. They rely on speed and coördination rather than strength. Such men usually have good defenses, and receive less punishment than cruder fighters, but they also seem less able to "take it." What would be a knock-out blow to their more highly developed nervous systems might be taken without much apparent damage by one of the brute type. The decline of the skilled boxer, when it finally comes, is often acute, and a single severe beating may result in marked decrease in fighting ability. This deterioration is chiefly in loss of speed and coördination. In the cruder boxers, speed and coördination have not been such important factors, and they continue along

on their "punch" after their finer control is lost, suffering many beatings before they are finally "through."

With reference to the incidence of punch-drunk, competent followers of the sport estimate that about 5% of men who remain in the professional ranks for a period of 5 years or more will become definitely punch-drunk. About 60% of fighters remaining in the ring for this period will develop mental and emotional changes which are obvious to people who knew them previously. A few deteriorate to the extent that institutionalization is necessary. Punch-drunk is said to occur among professional football players also.

In punch-drunk the prominence of objective mental changes and the freedom from symptoms are in contrast to the post-concussion syndrome in which subjective complaints are prominent, and objective mental changes are not often seen. In a survey of cases of gross brain traumas showing sequelæ, Glaser and Shafer found that over 80% were troubled by subjective symptoms, usually headache and dizziness, while "mental changes, consisting in disorders of the mental faculties with changes in character and habits, and associated with unreasonable and purposeless action and language" appeared in 9%, usually at an interval of months after the injury.[5]

Little information is available concerning the actual anatomic changes in punch-drunk. The explanation of this syndrome must be based on analogy and conjecture. Even the pathology of the common concussion is still disputed, although extensive clinical and laboratory studies have been made on this syndrome. Many authors have abandoned the stand that concussion is a transient disturbance of function without anatomic basis, and believe that it depends upon a permanent change resulting from multiple punctate hemorrhages through the brain substance.[6–10] These hemorrhages fill the perivascular spaces and, if large, infiltrate the surrounding nervous tissue. The neurones in the areas of these hemorrhages are damaged with subsequent degeneration. Organization and gliosis follow, with ultimate resorption of the glia cells and contraction of the glia fibers. This destruction of white and gray matter eventually results in shrunken convolutions, widened gyri, dilated ventricles and an enlarged subarachnoid space, with increase in the amount of cerebrospinal fluid. Small hemorrhages in the subarachnoid space are followed by local reactions, and subsequent pial-cortical adhesions.[9] Fay regards the decreased size of the brain in post-concussion cases as a result of pressure atrophy following deficient cerebrospinal fluid absorption.[11] Others believe it to be due to an increased production of fluid.[12] Some later writers have pointed out the similarity of this pathologic process to that seen in encephalitis, and have referred to it as "traumatic encephalitis." Clinical studies show much resemblance between post-concussion cases and some cases of encephalitis. Enceph-

alography in these post-concussion cases reveals extensive cortical or cerebral atrophy, external and internal hydrocephalus, and arachnoiditis, with obstruction to various cerebrospinal fluid pathways.[10, 11, 13] Of two encephalograms made on cases of punch-drunk under my observation, one showed no demonstrable changes. The other revealed definite cortical atrophy, which was localized to the left frontal region, rather than being diffuse in distribution. Since the injection of air into the subarachnoid space for encephalography relieves the subjective symptoms in about one-half of post-concussion cases, it is believed that the complaints are due to the arachnoiditis rather than to other pathologic changes. The absence of distressing local symptoms in punch-drunk is evidence against the presence of arachnoiditis.

Although multiple punctate hemorrhages probably constitute the underlying pathologic change in punch-drunk, extensive degeneration might be explained even without reference to such vascular lesions. It is hardly possible that a blow which jars the brain sufficiently to cause loss of consciousness would not be followed by some tissue reaction, such as hyperemia and edema with effusion into the intracellular spaces, leading to disturbances of nutrition and thus to impairment of function. An area with anatomic predilection to this type of injury is the midbrain. With a jar of the skull, the midbrain is forced against the sharp edge of the tentorium and bruised, resulting in edema and hyperemia. Following repeated insults to this region a gliosis may begin, and increase with each succeeding trauma. This scarring could result in a narrowing of the aqueduct, predisposing to the formation of an internal hydrocephalus with an increase in the intraventricular pressure and subsequent damage to the cortex.

Another explanation is that the jarring of the brain by a blow results in the fracturing of cell processes. The unequal specific gravities of the gray and white matter give to them different degrees of acceleration in response to a force. This inequality of movement might cause a rupture of the neurones at the junction of the two tissues.[14] The technical problems of demonstrating such minute lesions and differentiating them from artefacts leaves this occurrence unproven. The theory that functional changes may be based on a molecular disturbance or direct mechanical effect in the structural equilibrium of the cell likewise finds basis in the fact that protoplasm is an emulsoid containing lipoids, large protein molecules, and electrolytes in a watery base, and that these materials, having different specific gravities, will assume new relative positions in response to a violent movement, so that the cell cannot function normally.[15, 16]

However, the bizarre nondescript clinical picture seen in punch-drunk can probably best be explained on the basis of the small discrete vascular lesions which have been described. After pre-

senting a detailed neurologic analysis of 3 cases of punch-drunk, each having advanced physical disability, Parker summarizes, "The clinical picture in each case was very complex and it differed in one case from the others. The only agreement, however, was in the suggestion of diffuse or scattered lesions of the brain affecting different systems at one and the same time."[2] Jokl and Guttmann[3] conclude their paper on neuro-psychiatric studies on boxers with, "There are found organic symptoms which appear to the layman as dementia. A study reveals in many such cases various focal symptoms, reflex differences, disturbances in coördination and speech anomalies."

Comment. It is probable that no head blow is taken with impunity, and that each knock-out causes definite and irreparable damage. If such trauma is repeated for a long enough period, it is inevitable that nerve cell insufficiency will develop ultimately, and the individual will become punch-drunk.

The cognizance and investigation of this condition by the medical profession would be a contribution to the neurologic and psychiatric study of traumatic disorders. But a higher end would be the education of the layman to the remote dangers incident to repeated minor head traumas. The occurrence of this type of degenerative brain change must be recognized and publicized rather than disregarded and discounted. It is especially important that athletes entering into competitions in which head injuries are frequent and knock-outs are common should realize that they are exposing themselves not only to immediate injury, but also to remote and more sinister effects.

Summary. The clinical syndrome of punch-drunk is delineated by presenting a typical composite case study. The etiology and incidence are discussed, and the pathology is suggested.

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THE RECOVERY OF BRUCELLA ABORTUS FROM THE STOOLS OF HEALTHY CARRIERS.

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Brucella abortus can be recovered from the stools of a certain number of cases of undulant fever. Leavell, Poston and Amoss[1] observed, in a small number of carefully studied patients, that the organisms persist in the stools of chronic and recurring types of abortus infection. In the past 2½ years, in the Strong Memorial and Rochester Municipal Hospitals, the stools from 7 patients with this disease were cultured by a modification of the technique described by Amoss and Poston.[2] From four of these stools, brucella organisms were recovered.

The purpose of this study was to determine whether Br. abortus could be recovered from the stools of apparently healthy individuals, or from the stools of patients suffering from diseases other than clinically recognizable undulant fever, and also to describe a modification of the Amoss and Poston technique for the isolation of Br. abortus from stools. This method substitutes guinea pig inoculation for plate inoculation.

Material and Method *Material.* At the time that this investigation was planned, two studies were in progress which aided materially in the selection of suitable cases for study. All samples of blood, submitted to the Rochester Health Bureau Laboratories for the Wassermann test, were examined for abortus agglutinins. Simul-

taneously, intradermal tests with an abortus antigen were being made on a group of unselected patients. These studies made it possible to pick out a number of patients without clinical evidence of undulant fever, but with laboratory findings specifically indicative of Br. abortus infection.

Stools were obtained from 219 patients grouped as follows:

GROUP 1. Three hundred and thirty-two unselected hospital patients were tested for cutaneous reaction to an antigen prepared from Br. abortus No. 80. The organism was grown on liver infusion agar for 96 hours, after which the growth was removed and twice washed with physiologic saline. The bacterial suspension was centrifuged and, after discarding the supernatant fluid, the sediment was frozen and dried *in vacuo*. The dry material was then ground in a ball mill for 8 weeks. To the dry powder so obtained, physiologic saline was added and the grinding continued for 48 hours, this time in the icebox. The resulting suspension was filtered through a Berkefeld N candle. The final water-clear filtrate contained 13.3 mg. of nitrogen per 100 cc. It was standardized by repeated skin tests on a number of recovered cases of undulant fever and on several individuals with known sensitivity to abortus antigens, but with no clinical history of the disease. It was found that 0.1 cc. of 1 to 100 dilution of the filtrate gave a distinct erythematous reaction, without local necrosis and without the constitutional effects encountered with other antigens.[3, 4, 5]

Thirty-four (10.1%) of the 332 patients tested with the above described antigen gave positive cutaneous reactions. This percentage compares favorably with the number of reactors in this community previously determined with other antigens.[5]

From this group of 332 patients, stools were examined from each of the 34 patients who had a positive skin reaction and from 22 patients who gave negative reactions.

GROUP 2. Stools were collected from 139 patients whose sera had been tested for abortus agglutinins. Thirty-eight of these patients had anti-abortus agglutinins in their sera. Only 6 of the latter group were tested for cutaneous reactions. All were definitely positive.

TABLE 1.—AGGLUTININ TITERS FOR BR. ABORTUS OF 38 PATIENTS FROM WHOM STOOLS WERE AVAILABLE.

No. of patients.	Titer.
8	1 to 60
8	1 to 80
11	1 to 160
3	1 to 320
4	1 to 640
2	1 to 1280
2	1 to 2560

The sera from the remaining 101 patients in this series contained no abortus agglutinins.

GROUP 3. Stools were obtained from 24 patients whose sera were not examined for Br. abortus agglutinins, on whom skin tests were not performed and concerning whom no information of a possible abortus infection is available.

Method of Stool Examination. From 2 to 4 gm. of a fresh stool specimen were emulsified in 50 cc. of physiologic saline solution. This suspension was centrifuged at a low speed to remove the coarse particles. To the decanted fluid was added 0.5 cc. of an anti-abortus serum with an average titer of 1 to 640. The tubes were then incubated in a water bath at 37° C. for 2 hours, and again centrifuged at low speed for 5 minutes. After discarding the supernatant fluid, the sediment was emulsified in 2 or 3 cc. of physiologic saline and 0.25 cc. injected subcutaneously into each groin of a guinea pig. In all, 379 guinea pigs were inoculated. Pairs of animals were inoculated from each of 160 stools, while only one animal was used for each of the remaining 59 samples. From 25 to 35 days after inoculation, the guinea pigs were etherized, bled from the heart, and examined postmortem for evidence of abortus infection. The sera were examined for abortus agglutinins, using a saline suspension of living Br. abortus No. 80 as the antigen. The spleens were removed aseptically and cultured by planting pieces of tissue from 3 to 5 mm. in diameter on glucose ascitic blood agar. The cultures were incubated in an atmosphere of 10% CO_2 at 37° C. for 10 days.

To check the dependability of this method for recovering Br. abortus from stool emulsions, 5 stools, to which a few drops of a living abortus culture had been added, were included in this series. In each case Br. abortus was recovered from the animals.

Certain stool specimens were stored in the icebox for from 12 to 36 hours before examination. The viability of Br. abortus in human excrement under such conditions not being known, it was studied as follows. A few drops of a living abortus culture (No. 80) were thoroughly stirred into a normal stool and stored in a pint fruit jar in the icebox at 8° C. Guinea pigs were injected with specimens from this stool, prepared according to the above technique, on the 2d, 6th, 19th, 64th and 150th days after storage. Br. abortus was recovered in each instance. Cameron[6] has similarly found that Br. abortus survives for long periods in cow manure.

RESULTS. Organisms of the genus Brucella were recovered from 2 of 219 stools examined. The first positive specimen was obtained from a woman aged 54, who gave a history of ingesting raw goats' milk over a period of years in her youth. Her serum had an anti-abortus agglutinin titer of 1 to 60. This patient was afebrile at the time the specimen was obtained and had neither signs nor symptoms suggestive of brucellosis.

The second stool was secured from a patient about whom no data were available, except that she did not have clinical undulant

fever at the time the stool was obtained. Unfortunately, the patient is no longer under observation.

Discussion. This study of stools obtained from 219 patients indicates that individuals without febrile illnesses, without clinical suspicion of undulant fever, and without a history of the disease, may discharge Br. abortus from the intestinal tract.

Seventy-two of the 219 stools examined were obtained from patients who showed either abortus agglutinins in their sera, or a positive cutaneous reaction. Of the 38 patients with positive agglutinations, 17 had "reasonably adequate histories" of exposure to abortus infection. Twenty-four of the 34 patients with positive skin tests had similar histories. By "a history of adequate exposure" is meant either the ingestion of raw cows' or goats' milk for prolonged periods, or contact with cattle, goats or swine.

The viability of Br. abortus in a normal human stool, stored in a fruit jar at 8° C. for over 4 months, is of considerable interest.

Summary. 1. Brucella abortus was recovered from 2 of 219 stools obtained from patients who were not suspected clinically of having undulant fever.

2. Guinea pig inoculation of the stool sediments was substituted for the plate culture method of Amoss and Poston.

3. Brucella abortus, when mixed with human feces and stored at 8° C., remained viable for at least 150 days.

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BOOK REVIEWS AND NOTICES

THE MICROSCOPIC ANATOMY OF VERTEBRATES. By GEORGE G. SCOTT, PH.D., Professor of Biology in the City College, New York City, and JAMES I. KENDALL, PH.D., Instructor in Biology in the City College, New York City. Pp. 306; 167 illustrations. Philadelphia: Lea & Febiger, 1935. Price, $3.75.

MOST textbooks of microscopic anatomy and histology deal chiefly with human material; they are written to meet the requirements of the student of medicine. The authors of this book present a survey of the microscopic anatomy of vertebrates in general. The text is concise, clearly written and illustrated by a number of very useful diagrams and photomicrographs. Selected references to recent literature are appended to each chapter. This is a good book for the college student who is taking a pre-medical course or a course in general biology; the more advanced student will find discussed a variety of subjects not usually included in the shorter texts on biology. B. L.

OBSTETRICAL PRACTICE. By ALFRED C. BECK, M.D., Professor of Obstetrics and Gynecology, Long Island College of Medicine; Obstetrician and Gynecologist-in-Chief, Long Island College Hospital, Brooklyn. Pp. 702; 1053 illustrations. Baltimore: The Williams & Wilkins Company, 1935. Price, $7.00.

THIS new book on "Obstetrical Practice" gives, in a refreshingly simple manner and with a decided personal tone, the basic principles of obstetrics as taught in the Long Island Medical College. The conciseness of text, and the directness of treatment suggested, has much of benefit for the student or general practitioner, who needs guidance in obstetrical thought and therapy. For those who wish to read further there is appended to each chapter an excellent bibliography.

Of especial value are the discussions of Factors in Labor, the Mechanism of Labor and the Clinical Course of Labor. A conservative treatment of eclampsia is recommended; the author's mortality under this therapy is 6.5%. Throughout the book important points have been emphasized in heavy type, and nowhere to greater advantage for the practitioner than in the chapter on posterior presentations of the occiput. The author considers Braxton Hicks' version the best general treatment for placenta previa but gives his reasons for individualizing treatment by other methods.

Contracted pelves are considered under a modification of the classification of Caldwell and Moloy. The profuse use of line drawings in the enormous number of illustrations in the book serves to good advantage in the discussion of operative obstetrics. Here there are given definite indications and requisites for each operation. The advantage of the low-flap section is emphasized.

On the whole this new book is an excellent exposition of the views and teachings of a writer well qualified to express his individual opinions. The well-written straight forward discussions will make it of value to both students and practitioners. P. W.

THE MEDICINE-MAN OF THE AMERICAN INDIAN AND HIS CULTURAL BACKGROUND. By WILLIAM THOMAS CORLETT, M.D., L.R.C.P. (LOND.), Professor Emeritus of Dermatology-Syphilology, Western Reserve University; Fellow of the Royal Society of Medicine of Great Britain, etc. Pp. 369; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $5.00.

ENTHUSIASTS of the aboriginal in the western hemisphere will find in this book, for all its informal and leisurely tone, all the absorbing interest its title promises. A generous and always judicious use of quotation from the literature of several centuries lends it many of the advantages of a well-edited anthology. But the author writes also out of a personal interest and experience that began early in his own career. The result is a book full of information imparted with a charm seldom found in such works. Save in the historic sense, it is, of course, not a strictly medical subject, since the medicine-man practised less medicine than shamanism, and ritual or trance were his treatment or his consultation. There are chapters On Indian Diseases, on Childbearing, and on Foods and Materia Medica, but the main body of the text treats *seriatim* the anthropologist's 15 culture areas of the Americas in the light of the practices and beliefs of their healers, who were, quite as much, also their priests. The author gives an engrossing account of the regional varieties of the healing art, that ritual through which the common tribespeople shared a little in the darker mysteries of their medicine-men. The book closes with a deeply felt lament for the passing of a great race and, with them, of things strange and dim that history may never be able to fix in its clear record.

H. B.

MAN, THE UNKNOWN. By ALEXIS CARREL. Pp. 346. New York: Harper & Bros., 1935. Price, $3.50.

FOR a general rather than any special audience, the author has undertaken to supply that heroic need, a synthesis of all that men know of themselves. Many of his already numerous readers will have considered that more than due regard is had also for what men have ground to hope for in one another: latent possibility is here treated as a coördinate of scientific truth; only the addition of potential to actual can yield even a rough estimate of the sum of all. Though in manner and method achieving all possible simplicity, it is yet a book whose enormous variety and compression of content is unlikely to satisfy either the too ignorant on many counts, or the very learned (certainly not the very opinionate) on any one. There are passages assured of offensiveness to the "orthodox" in politics, religion, science. Some readers may even be inclined to lay the book aside on the quite incidental provocation of its syntax—prevailingly declarative, even to the point of apparent dogmatism when the reader is in disagreement. According to the author's own apologia, however, almost every sentence, because of the vastness of the subject, must summarize the achievements of at least one man's whole lifetime of research; hence the book's effect of unremitting assertion.

The ordering of this immense complex of data has that fine clarity which comes as no surprise in a writer of the author's nationality. Not the handling, but the selection, the admission, of data, and the critical judgments passed upon them, are what here and there give pause. Probably but few of the author's confrères in science will have anything short of high praise for the central section of the book—its chapters summarizing present doctrine in the sciences of the body and those of the mind, its other chapters treating of Inward Time in its aspects physiologic and psychologic, of Adaptive Functions (their necessity for the development of personality,

their general neglect and actual atrophy in our civilizations). But there are frequent passages in which the author looks toward the future and prescribes for it, oft invoking the as yet unaccredited infant science of "metapsychics;" and in these his diagnosis of the human condition has more often the note of some prophet of old than of the contemporary clinician. Most of his readers will not be left with much doubt that the sickness charted is real, nor will many of them be at once agreed to submit to the drastic operation proposed. It will take much time and research to learn whether the author is wholly right about the mass of controversial matter upon which his own mind is decided even when it appears not to be consistent, yet the sum of knowledge and theory that he offers is so vast and broad and basic that the question of his being wrong in fundamentals scarcely arises, unless in the respect of their explicit application. Beset by these enigmas, each reader will decide for himself as he can, whether the author carries conviction when he tells us, in effect, that, after the grand unsuspected discoveries of the past, will come other "impossibles," other unbelievables, which may—now, ages hence, or perhaps after all never, depending on our and our progeny's development of the human psychesoma's capacities—comprise the commonplace possessions of the race.

H. B.

MODERN OFFICE AND GENERAL PRACTICE. A Handbook of Practical Medicine. By DEANE R. BRENGLE, M.D. Pp. 320; illustrated. Kingsport, Tenn.: Southern Publishers, Inc., 1935. Price, $3.25.

AN encyclopedic arrangement of therapy in general practice.

The author anticipates the criticism of those whose opinions may differ from his by stating that he has put to clinical test each procedure recommended. However, the urologists, dermatologists and surgeons probably will not agree that certain of his suggestions should be followed by the general practitioner. The composition is more practical than scholarly. There are three interesting sections dealing with medical economics. The absence of any discussion of the anemias is a notable omission.

W. J.

IMMUNOLOGY. By NOBLE PIERCE SHERWOOD, PH.D., M.D., Professor of Bacteriology, University of Kansas, and Pathologist to the Lawrence Memorial Hospital, Lawrence, Kansas. Pp. 608; 27 illustrations, 8 colored plates and many tables. St. Louis: The C. V. Mosby Company, 1935. Price, $6.00.

THIS book should prove useful to medical students in conjunction with a regular laboratory course in immunity, as well as to graduates as a reference work, since it is largely made up of abstracts of the fundamental sources of immunologic knowledge to the date of publication. The book supplements textbooks of bacteriology, many of which are unnecessarily exhaustive studies for the second-year medical student.

The extreme detail concerning the technique of laboratory diagnosis of syphilis belongs in a manual of laboratory methods rather than in an introduction to the study of immunity. Sixty-seven pages on complement fixation seems too much in a book of this sort when such important work as that on influenza virus of Andrewes, Laidlaw and Smith, in England, and of Francis and Shope, in this country, is not mentioned specifically. There is also no mention, possibly because it is so recent a development, of the preservation of antisera in the dried "lyophil" form which is being used in the treatment of a variety of infectious diseases in several serum exchanges.

The book is very well printed and bound. The illustrations, diagrams and tables are clear and useful.

The author's style of writing is lucid, fluent and forceful. He has succeeded in presenting a difficult subject so clearly that the young student should be grateful to him for cutting away abundant underbrush.

H. P.

BEITRAG ZUR KENNTNIS DES ILEUM TERMINALE FIXATUM UND ILEUS ILEI TERMINALIS FIXATI. By LENNART PETERSON. Eine anatomische, klinische und klinischstatistische Studie. (Vol. 75, Suppl. 32 of Acta Chirurgica Scandinavica.) Pp. 113; illustrated. Helsingfors: Mercators Tryckeri Aktiebolag, 1934. (No price given.)

IN the first portion of this monograph Peterson has classified abnormalities of attachment of the terminal ileum and emphasized that one or more of them occur in over 16% of individuals. The most common abnormality is a low attachment of the mesentery of the terminal ileum. Rarer but more familiar types are the Lane kink and Jackson's membrane (when the latter is attached to the ileum).

The fact that these anatomic variants have received so little attention in the past would seem to be explained by the author's statement that most of the cases are asymptomatic and cannot be diagnosed without abdominal section. There appears to be no relation between Ileum Terminale Fixatum and the incidence of appendicitis.

Its chief importance lies in the occurrence of ileus as a complication. Ileus Ilei Terminalis Fixati may arise by several different mechanisms such as kinking and volvulus. These are considered in detail in the second portion of the monograph. A study of reports from all parts of the world suggests that the particular form of ileus that occurs, is partly determined by the patients racial background, volvulus being more common in the East European peoples than in the West European and North American groups.

Although the author's experience indicates an incidence of ileus in 1.1% of cases of Ileum Terminale Fixatum, he was able to find only 120 clearly described cases in the literature. In his analysis of 2 series from Finland (185 cases, 1915–1930, and 31 cases, 1931–1932), the mortality was reduced from 59.5% to 45.2% in the second series.

The monograph is exceedingly thorough and should lead to a more fundamental understanding of a number of cases of acute intestinal obstruction occurring in the right lower quadrant. An English summary affords a terse if not very idiomatic introduction to the subject. I. R.

A HISTORY OF SCIENCE, TECHNOLOGY, AND PHILOSOPHY IN THE 16th AND 17th CENTURIES. By A. WOLF, Professor and Senator, University of London; Head of the Department of History and Methods of Science, etc., with the coöperation of Dr. F. DANNEMANN, Professor in the University of Bonn, and MR. A. ARMITAGE, of University College, London. Pp. 692; 316 illustrations. New York: The Macmillan Company, 1935. Price, $7.00.

WHILE there may be much difference of opinion as to when the Middle Ages were finished, there is no doubt but that the 16th and 17th centuries witnessed the birth and marvelous growth of modern lines of thought and scientific discovery. It is fortunate for the reading world that the requirements of students pursuing courses in the history, methods and principles of science in the University of London have led the possessor of such encyclopedic knowledge and lucid style to give this detailed and well-

documented account. We subscribe to the author's "belief that the world has need of a new intellectual reorientation, and that to this end a close study of the history of human thought in its most objective spheres would be the best beginning." In addition to Astronomy, Mathematics, Physics Chemistry, Meteorology, Geology, and the biologic sciences, the author has included Geography, four chapters on Technology, Psychology, the Social Sciences and Philosophy. Such wide scope means that even in a book of these generous dimensions many subjects must be treated illustratively—as one soon learns on perusing one's own field—but the selections are well made and a happy medium struck between the occasional detail needed for a readable story and the masses of facts "required for" a reasonably full account. The abundance of carefully selected and for the most part well-reproduced illustrations adds further to the interest and value of this notable volume. It is to be hoped that the contemplated volumes on the 18th and 19th centuries and on the ancient and mediæval periods will be equally instructive and entertaining. E. K.

LOCALIZED RAREFYING CONDITIONS OF BONE. As Exemplified by Legge-Perthes' Disease, Osgood-Schlatter's Disease, Kümmell's Disease and Related Conditions. By E. S. J. KING, M.D., D.Sc., M.S. (MELB.), F.R.C.S. (ENG.), F.R.A.C.S., Honorary Surgeon to Out-Patients, Melbourne Hospital; Stewart Lecturer in Pathology, University of Melbourne. Pp. 400; 70 illustrations. Baltimore: William Wood & Co., 1935. Price, $7.50.

THIS well-written and elaborately documented monograph is comprised of "the greater part of the material which was submitted for the Jacksonian Prize of the Royal College of Surgeons in 1933." It is divided into four Sections:

Section I considers the formation of bone; its structure, composition, development and physiology. The pathology of bone rarefaction and abnormal calcification, together with the interpretation of the roentgenography of these processes, is also dealt with.

Section II deals with those localized rarefying changes in bone known as the osteochondritides. These changes are considered from their anatomic localization. This section comprises 197 pages and is the largest of the monograph.

Section III deals with posttraumatic rarefaction, both localized and diffuse.

Section IV chiefly considers rarefaction of the articular surface when associated with loose bodies in the contiguous joint.

The value of this book lies in that the author has brought together under a common heading a large number of heretofore isolated bone lesions. These lesions had cluttered the literature and confused the student through their designation by the name of the author first describing them. Some of the lesions reflected the nationalism of medical science by being weighted with the names of more than one "first describer," as in the case of Legge-Calvé-Perthes-Waldenström's disease of the proximal epiphysis of the femur.

That these epiphysial rarefactions were not a number of isolated diseases but constituted a single pathologic process occurring in different localities has been long known. The Reviewer has so dealt with them in his lectures during the past 6 years.

Little new has been developed by the author relative to the osseous lesions discussed. His work has been mainly one of erudite scholarship as con-

sidered from the standpoint of bibliographic research. This work he has performed splendidly though not, as he states, exhaustively.

To the great majority of clinicians and to many pathologists the author's monograph will bring clarity in a formerly confused section of bone pathology. For some time to come this monograph will be the definitive work on the osteochondritides. G. W.

JOHN WHITRIDGE WILLIAMS. Academic Aspects and Bibliography. By J. MORRIS SLEMONS. Pp. 109; 1 illustration. Baltimore: The Johns Hopkins Press, 1935. Price, $1.50.

THE author has performed a useful service in publishing in book form this presidental address before the Pacific Coast Society of Obstetrics and Gynecology. With the bibliography, Williams' contribution, it is now possible for many who never knew Williams in the flesh to become acquainted with the man who perhaps contributed more than any one else to scientific obstetrics during the past 30 years. Slemons has written here as an ardent student rather than as an experienced biographer; but still has done much to acquaint the world with the greatness of a very fine man. One must be impressed by the keenness of Williams' mind, as indicated by the range of his writing and by his energy when one sees a bibliography of 137 papers, not including his other more unofficial contributions.

A desirable addition would be more detail about Williams as the man rather than as the scientist. The human side is always more interesting than the intellectual to the average reader. It is hoped that the author may be persuaded to write a more extended biography sometime in the future. D. M.

NEW BOOKS.

Atlas of Pathological Anatomy, Vol. 2. Issued under the Direction of the Editorial Committee of the British Journal of Surgery. Compiled by E. K. MARTIN, M.S., F.R.C.S. Pp. 475; 268 illustrations (168 in colors). Baltimore: William Wood & Co., 1935. Price, $15.00.

Die Liquordiagnostik in Klinik und Praxis. By DR. HANS HEMME, Privatdozent für Neurologie, Chefarzt der neurologischen Abteilung des Allgemeinen Krankenhauses Barmbeck in Hamburg. Pp. 205; 96 illustrations. München: J. F. Lehmanns, 1935. Price, Mk. 7.

International Clinics, Volume 1. Forty-sixth Series, March, 1936. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 314; illustrated. Philadelphia: J. B. Lippincott Company, 1936.

This 46th Series begins with an unusually eminent list of authors and a great predominance of medical subjects. Of especial interest to the Reviewer were the opening comprehensive article on Simmonds' Disease, suggestive papers on secondary and pernicious anemia, and the medical progress review of phosphatase activity and calcium and electrolyte metabolism.

Endocrine Tumours and Other Essays. By FREDERICK PARKES WEBER, M.A., M.D., F.R.C.P., F.S.A., Senior Physician to the German Hospital, London. Pp. 207. London: H. K. Lewis & Co., Ltd., 1936. Price, 7s. 6d.

The Phenomena of Life. A Radio-Electric Interpretation. By GEORGE CRILE. Edited by AMY ROWLAND. Pp. 379; 113 illustrations and 22 tables. New York: W. W. Norton & Co., Inc., 1936. Price, $3.50.

Twentieth Century Psychiatry. Its Contribution to Man's Knowledge of Himself. By WILLIAM A. WHITE, M.D., A.M., Sc.D. Pp. 198. New York: W. W. Norton & Co., Inc., 1936. Price, $2.00.

Foundations of Short Wave Therapy. Physics—Technics—Indications. Physics and Technics by WOLFANG HOLZER, DR. MED., Assistant in the Physiological Institute of the University of Vienna. Medical Applications by EUGEN WEISSENBERG, DR.MED., Medical Superintendent of the Short Wave Section of the University Clinic for Nervous and Mental Diseases in Vienna. Translated by JUSTINA WILSON, F.R.C.P. (EDIN.), D.M.R.E. (CANTAB.), and CHARLES M. DOWSE, B.Sc. ENG. (LOND.), A.M.I.E.E. Pp. 228; 53 illustrations and 10 tables. London: Hutchinson & Co., Ltd., 1936. Price, 12/6.

Insulin. Its Production, Purification and Physiological Action. By DOUGLAS W. HILL, B.Sc. (BRIS.), PH.D. (LIV.), Lecturer in Chemistry, University College, Exeter; Special Lecturer in Organic Chemistry, University of Bristol, and FREDERICK O. HOWITT, M.Sc., PH.D. (LOND.), F.I.C. Foreword by PROFESSOR E. C. DODDS. Pp. 219; 6 photomicrographs and 7 tables. London: Hutchinson & Co., Ltd., 1936. Price, 12/6.

The Specificity of Serological Reactions. By KARL LANDSTEINER, M.D., The Rockefeller Institute for Medical Research, New York City. Pp. 178. Springfield, Ill. Charles C Thomas, 1936. Price, $4.00.

Seuchenentstehung und Klimaforschung. Die Ergebnisse der Klimaforschung in Ihrer Bedeutung für die Epidemiologie. By DR. MED. FRIEDRICH WOLTER, Leiter des Hamburgischen Forschungsinstituts für Epidemiologie. Pp. 43; 9 tables. Stuttgart: Hippokrates-Verlag G.m.b.H., 1936. Price, RM. 3.75.

The author tries to show that epidemic diseases are miasmatic in nature, and that they are caused by changes of the soil and of the climate.

Die Entstehungsursachen der Haffkrankheit. In dem Zeitraum von 1924–1933 vom epidemiologischen Standpunkt. By DR. MED. FRIEDRICH WOLTER, Leiter des Hamburgischen Forschungsinstituts für Epidemiologie. Pp. 56; 2 tables. Stuttgart: Hippokrates-Verlag G.m.b.H., 1936. Price, RM. 4.50.

This is an attempt to show that the "Haffkrankheit" is a rare type of the epidemic disease, the miasma causing it being a gas formed in the water of the bay polluted by the waste waters of Königsberg.

Les Parathyroïdes. First Fascicle, Volume 2, of Traité d'Endocrinologie. By C. I. PARHON, Professeur à l'Université de Jassy, and M. GOLDSTEIN, Docent à l'Université de Bucarest. Pp. 524; illustrated. Jassy: H. Goldner, 1935. Price, francs 40.

NEW EDITIONS.

An Index of Differential Diagnosis of Main Symptoms. By various writers. Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D. (OXON.), F.R.C.P. (LOND.), Consulting Physician to Guy's Hospital; late Physician to H. M. Household. Pp. 1145; 742 illustrations, of which 196 are colored. Fifth Edition. Baltimore: William Wood & Co., 1936. Price, $16.00.

A Guide to Psychiatric Nursing. By F. A. CARMICHAEL, M.D., Superintendent, Osawatomie Hospital, Osawatomie, Kansas; Lecturer in Clinical Psychiatry, University of Kansas Medical School, Kansas City, and JOHN CHAPMAN, M.A., M.D., Sometime Associate in Psychiatry, Osawatomie State Hospital, Osawatomie, Kansas. Pp. 175; 31 illustrations. Philadelphia: Lea & Febiger, 1936. Price, $2.25.

Dental Infection and Systemic Disease. By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division, Cleveland Clinic, etc. With a Foreword by DR. EDWARD C. ROSENOW. Pp. 163; 63 illustrations. Philadelphia: Lea & Febiger, 1936. Price, $2.50.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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THROMBOPENIC PURPURA AND SOME OTHER HEMORRHAGIC DISEASES.

In the past few years there has been renewed interest in hemorrhagic diseases, which has resulted in a change of concepts regarding their etiology and treatment. There has also resulted a rather indiscriminate use of hemostatic agents, which has served to confound rather than to clarify understanding. In many reports data are inadequate and poorly controlled. Consequently one is forced to accept new remedies with cautious conservatism.

I. Thrombopenic Purpura.—The etiology of thrombopenic purpura is unknown. Older theories ascribing the disease to bone-marrow disturbance, either as a primary dyscrasia or as a reaction secondary to injury[1] have not been confirmed by subsequent study. There are also valid objections to the theory of splenic malfunction,[2] even though splenectomy provides striking benefit in most cases. Indeed, it is questionable whether platelets play an essential part in the causation or mechanism of thrombopenic purpura. Studies by Bedson[3] and Roskam[4] with platelet antiserum indicate a dual mechanism responsible for experimental purpura, dependent on thrombopenia and altered vascular reactivity. It is apparent, however, that clinical purpura occurs also without platelet changes, as in "anaphylactoid" purpura and scurvy, where the vascular component alone appears to be involved. Recent studies by Gratia and Linz[5] on the Shwartzman phenomenon suggest that the difference between local erythema with purpura and generalized purpura with thrombopenia and anaphylactic shock is quantitative rather than qualitative. Therefore, it is possible that thrombopenia, when it occurs, is simply another manifestation along with altered vascular reactivity of the same underlying state, and that the distinction between thrombopenic and non-thrombopenic purpura

is unwarranted. "The connection between capillary damage and thrombopenia may be reciprocal and the symptoms may follow a common insult."[6]

Current opinion, thus, suggests an allergic state as the cause of thrombopenic purpura. Although earlier observations by Osler,[7] Meleney,[8] and Alexander[9] indicated clearly such a mechanism in "anaphylactoid" purpura, it is only recently that thrombopenic purpura also has been included in this group. The present point of view has been supported by observations on known agents as arsphenamin, quinin, "sedormid," "nirvanol," milk and other foods, and possibly bacteria sensitivity to which has provoked thrombopenic purpura indistinguishable from "essential" thrombopenia. McCarthy and Wilson[10] reported 2 cases and reviewed 79 recorded in the literature of blood dyscrasias following arsphenamin injection. In one group of 12 cases, thrombopenic purpura alone developed without red cell or white cell disturbance. "All the cases of this group developed only after considerable treatment with numbers of injections, and it is probable that a specific sensitivity towards the arsphenamins gradually took place." Rich[11] described a similar case with thrombopenic purpura occurring abruptly after the sixteenth injection of neoarsphenamin, likewise with prompt recovery on withholding further arsphenamin injection. He attributed the reaction to a "destructive action" in the peripheral blood stream. Loewy[12] reported 3 cases of thrombopenic purpura following the prolonged administration of the hypnotic "sedormid." The drug had been taken in the usual therapeutic doses without harm. However, the patients acquired a sensitivity to the drug, described by the author as an "allergo-toxic" effect. Peshkin and Miller[13] observed a woman with thrombopenic purpura, which recurred four times under observation after administration of either quinin or ergot, although in childhood "quinin had been liberally administered with apparent tolerance." Jones and Jacobs[14] reported a case of thrombopenic purpura in a girl 9 days after onset of "nirvanol" therapy for chorea. Landsberger's[15] case of thrombopenic purpura was demonstrated to be due to sensitivity to cow's milk. Brinnitzer[16] reported a similar reaction in a child with thrombopenic purpura brought on twice following transfusion with compatible blood from the patient's mother. Squier and Madison[17] have demonstrated that specific sensitization to certain foods may be the cause of thrombopenic purpura in some cases. McLean and his coworkers[18] have observed 11 cases of thrombopenic purpura occurring 6 to 21 days after the subsidence of acute infection, "which suggests the possibility, clinically at least, that thrombocytopenia may be an allergic manifestation."

Thus it is implied that essential thrombopenic purpura may be a similar reaction to those enumerated but provoked by agents as yet unrecognized. Whether or not this concept is correct, it has served as a working hypothesis for the newer therapeutic measures. The aim, therefore, has been directed at two factors: 1, removal of the exciting agent, such as drugs; 2, alteration of the fundamental allergy or hypersensitive state. The second approach may be involved in the beneficial effects reported on the use of snake venom.

Snake Venom Therapy. Stockton and Franklin,[19] in 1931, reported the arrest of hemorrhage after injection of antivenin in a case of acute thrombopenic purpura, which had failed to respond to other therapy. Bothrops antivenin, a serum globulin obtained from blood of horses immunized against Bothrops venom was used. Because of previous horse serum therapy, the patient was desensitized first with two intracutaneous injections of 0.1 and 0.2 cc. respectively at half-hour intervals and then given 10 cc. of the antivenin subcutaneously. Bleeding stopped in 24 hours.

Taylor,[20] in 1933, reviewed 7 cases of thrombopenic purpura previously reported, as well as his own, treated by either crotalic or bothropic antivenin. There were 2 deaths and 5 recoveries. His method of administration was not stated precisely. Presumably 10 cc. of bothropic antivenin may be given intramuscularly, and this may be followed if necessary, by doses of 5 to 10 cc. for several days. "Provided sensitization to horse serum is not extreme, a trial of bothropic antivenin should, in the writer's opinion, be made in all cases before splenectomy is undertaken. In fulminating cases, it may be given intravenously, the usual precautions against protein shock being observed, in a dosage of 10 cc., repeated several times in 24 hours, if necessary, or at daily intervals." The data are insufficient as yet to judge the efficacy of this therapy. Its benefit is said to be derived from anti-hemorrhagins and anti-hemolysins.

Recently Peck and Rosenthal[21] reported an impressive series of cases of bleeding disorders treated with moccasin snake venom. Peck had observed, in 1931, that when this venom was injected into a rabbit, it rendered the animal refractory to a subsequent Shwartzman reaction. Because of the analogy of this reaction to clinical purpura, the subcutaneous injection of moccasin venom was tried in cases of purpura and in other diseases characterized by an abnormal bleeding tendency. Definite benefit was claimed in "anaphylactic" and "toxic" purpura, in several cases of thrombopenic purpura, as well as in the bleeding of multiple telangiectases, bronchiectasis, functional uterine bleeding, etc. The effect was ascribed to a change in the vessel walls. The mode of administration was as follows: moccasin venom was prepared in ampoule form as 1 to 3000 solution. The initial dose was 0.4 cc., injected subcutaneously in the arm or thigh. The amount was then rapidly increased to 0.8 or 1.0 cc. as a maximum dose, which usually was given twice weekly for 3 months. The patient's maintenance dosage was then determined according to the hemorrhagic symptoms. For children, the corresponding initial dose was 0.2 cc. and the maximum dose 0.6 cc. Many patients developed a local reaction of hypersensitivity to the venom after the fourth or fifth injection. In most cases this was overcome by reducing the following dose to 0.05 cc. of 1 to 3000 dilution, and at each subsequent injection increasing the amount until reaching the required dosage. Rarely greater dilution and more cautious desensitization was needed. This form of therapy needs further confirmation before it may be considered acceptable.

The venom of certain snakes is characterized by clot-accelerating ability on the formed elements of the blood. These venoms have been used locally to arrest accessible bleeding occurring in purpura, hemo-

philia and other bleeding conditions. MacFarlane and Barnett[22] have reported success with the Russell viper in 1 to 10,000 dilution, and Rosenfeld and Lenke,[23] with tiger snake venom in 1 to 5000 dilution. Activity was attributed to a thrombin-like substance.

Dietary Measures. In current articles on the treatment of purpura, stress is laid on the need of high vitamin, high protein diet, as well as of iron to help recovery from anemia of blood loss. Kugelmass[24] claimed benefit with a diet rich in protein and fat. However, there is little experimental or clinical evidence to justify this point of view. When the patient is undernourished such a régime is warranted, but purpura, in our experience, shows no predilection for undernourished persons, nor does the dietary of patients with purpura reveal itself characteristically low in vitamin or protein-containing foods.

Following the isolation of hexuronic acid from citrous fruits and from adrenal cortex by Szent-Györgi, in 1928.[25] there has developed widespread interest in the relationship between vitamin C metabolism and hemorrhagic disease. Apparently latent scurvy can be precipitated not only by insufficient intake of the vitamin but also by changes in the intermediary metabolism in the course of chronic infections[26,27,28] and probably by interference with absorption, as in disease of the gastro-intestinal tract. It may be that certain cases of "purpura" occurring under such conditions are in effect scurvy, and that vitamin C therapy would be beneficial. Because of its relationship to the integrity of bloodvessels, vitamin C has been administered also in other bleeding disorders. Vogt[29] reported the arrest of uterine hemorrhage in 4 young women, 1 of whom had thrombopenic purpura, by the intravenous injection of cevitamic acid. Junghans[30] claimed to have arrested hemorrhage in 33 of 35 patients with severe menorrhagia, mostly of the premenopausal type, with 100 mg. of cevitamic acid injected daily intravenously. Bleeding stopped in 4 to 6 days. Böger and Schröder[31] reported that they had checked bleeding in every class of hemorrhagic diathesis, including thrombopenic purpura, by the intravenous injection of 100 to 300 mg. of cevitamic acid daily. These claims appear extravagant to us. In our hands, at least, this therapy has been of no value in the treatment of thrombopenic purpura.

Transfusion. In a certain number of cases spontaneous recovery occurs. Because of this a conservative[18,32] attitude towards purpura has been advocated. Large direct or whole blood transfusions[33] have been advised. Jones and Tocantins[32] observed that daily transfusions of 200 to 300 cc. are usually more beneficial than isolated large transfusions in checking the hemorrhage of purpura. This also has been our experience. Citrated blood apparently is as effective as direct, or whole blood transfusion.

Roentgen Ray. Roentgen ray therapy directed over the spleen has been advocated for many years.[34] Recent reports by Hippe and Kochmann[35] and others record gratifying results. Other reports are less favorable. The differences may be due to the selection of cases and to the varying modes of administration. In our experience, this form of therapy has been disappointing.

Splenectomy. Eliason and Ferguson,[36] reviewing 213 cases in the literature up to 1932, found that 88% of patients with chronic thrombopenic purpura and 65% of those with the acute forms were cured by splenectomy. The operative mortality of the entire group was 13%, whereas in the last 4 years the operative mortality had been 7% in 113 cases. The higher figure was attributed to the poor operative risk of the earlier group of patients. The authors emphasized the need of preparation by transfusion in these patients. There still remains controversy over the optimal time for splenectomy. Conservative judgment suggests the advisability of waiting for temporary remission. However, "uncontrollable bleeding, whether sudden and severe or recurrent, appears to be the indication for splenectomy in purpura hemorrhagica."

II. Bleeding Tendency in Obstructive Jaundice.—The bleeding tendency in jaundice has been attributed to lack of available calcium, retention of bile constituents, decreased fibrin or fibrinogen, excess of heparin, etc., but later studies have not confirmed such hypotheses. The extensive literature on this subject is reviewed in articles by Wangensteen[37] and others[38–41]. Recently anoxemia,[39] and lack of prothrombin,[40] and excess of cystein[41] have been suggested as causes of the phenomenon. Since the mechanism is not clearly understood, the prediction of hemorrhage in jaundiced patients has been uncertain. Apparently as increased sedimentation rate, described by Linton,[42] is not a constant feature in these cases.[38,43] Certain authors [38,44] believe that the intensity and duration of jaundice and a prolongation of clotting time are a better index of the bleeding tendency. Quick[40] and others believe that it may be detected by a prolonged prothrombin time.

Notwithstanding theoretical objections to calcium therapy, there are still many who attest to its efficacy, either in the form of calcium chlorid, as proposed by Lee and Vincent[44] and Walters,[45] or in the form of the gluconate. Walters prepared patients with obstructive jaundice for operation by administering large amounts of glucose by mouth and by rectum, and also by injecting intravenously 5 cc. of a 10% calcium chlorid (prepared in redistilled water) daily for 3 days before operation. He believed that this prevented postoperative hemorrhage. However, probably the most reliable measure for preventing and combating hemorrhage in jaundice still appears to be transfusion. Judd[39] and his coworkers have pointed out that if surgery is indicated in jaundiced patients, it is advisable to force both enteral and parenteral glucose, and to give blood transfusions before and after the operation.

III. Hemophilia.—The mechanism underlying the prolonged clotting time and bleeding tendency in hemophilia is still unknown. Older theories attributed the abnormality to calcium deficiency,[46] to thrombokinase defect,[47] to excess of antithrombin,[48] and to prothrombin defect.[49] More recent work, however, suggested rather that the abnormality resided in a peculiar platelet stability resulting in a slow liberation of prothrombin (according to some) or thrombokinase (according to others) with consequent delay of clot formation.[50,50a] The defect, thus, has been laid to a qualitative change, and therapy accordingly has been aimed at acceleration of coagulation. Although accessible bleeding

apparently can be checked by local hemostatic agents,[22,23] attempts to alter the fundamental clotting defect have been unsuccessful. The beneficial effect of ovarian therapy, reported by Birch[51] has been disclaimed by other workers.[52] Until recently the most dependable method of shortening clotting time and checking bleeding has been transfusion of blood. In our experience, this usually can be done with small transfusions either of citrated blood or plasma.[53]

Recent studies by Eley[54] have been most promising for a specific therapeutic agent. Following the previous reports by Mills[55] that "tissue fibrinogen" prepared from bovine lung tissue shortened the clotting time and arrested the hemorrhagic phenomena in this disease, Eley prepared a tissue protein extract from human placenta which provided a more marked and lasting effect. With the oral administration of from 5 to 15 cc. of this material two to three times daily, the clotting time was reduced to normal limits for from 2 to 9 days. In 11 of 15 cases there was remarkable success. Older patients were apt to be refractory; in certain of these the intramuscular injection of 5 to 10 cc. of the material gave a satisfactory response. This material was also very effective in arresting accessible bleeding in other hemorrhagic conditions.

IV. Miscellaneous Hemostatic Agents.—In Europe, several new drugs have had recent vogue in the treatment of bleeding disorders. "Nateina," a proprietary which is said to be a mixture of vitamin concentrates and calcium phosphate, has been advocated for the treatment of hemophilia.[56] Reports have not been universally favorable.[57]

"Sangostop," a proprietary made of a solution of apple pectin, has been advocated for non-specific bleeding. It is marketed in 1.5% solution for parenteral use. Brahn and his coworkers[58] found that it shortened clotting time in rabbits. Sack[59] reported the prompt arrest of bleeding in 32 cases of hemorrhage after the injection subcutaneously or intragluteally of 20 to 80 cc. It was administered orally in 5% solution particularly for cases of gastric hemorrhage. In 3 patients with hemophilia there was also apparent benefit from this therapy.

Congo red in 1% aqueous solution has been administered with success in severe cases of thrombopenic purpura. Brühl[60] reported the prompt arrest of bleeding in 4 cases which had failed to respond to the usual measures. The dye was injected intravenously in doses of 10 to 20 cc. without causing untoward reactions. Bleeding stopped within 4 to 12 hours. Its mode of action was unexplained.

These agents may prove to be of distinct value. Unfortunately we have had no experience with them, and therefore an appraisal of their worth would be untimely.

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RADIOLOGY

UNDER THE CHARGE OF
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Lesions Involving the Lung and Pleura.—The necessity of knowing the exact position and shape of a lesion is a fundamental requisite to the proper interpretation of the roentgenographic images of lesions involving the lung. Levitin and Brunn,[6] in a study of the roentgenologic appearance of the lobes of the lung and the interlobar fissures, have provided a series of excellent illustrations depicting the free portions of the individual lobes and the overlapping portions in their relation to one another. In a series of 32 drawings they exemplify the various shadows observed in different types of lesion. Sixty-four reproductions of roentgenograms compare the findings in films made in the postero-anterior projection with those observed in those made in the lateral projection.

Roentgenograms exhibit superimposed shadows of a three-dimension object projected on a flat plane. The shadows are of two dimensions and do not give a true picture of the shape of the process and its location. To bring out the third dimension, stereo-roentgenograms are often made. The use of postero-anterior and lateral projections afford two films in planes at right angles to each other, which is of great aid in studying the position and shape of the parts under consideration.

Processes occurring in the interlobar septa offer particular difficulty in interpretation on a single postero-anterior projection. Because of the oblique position of the septa, the horizontal ray projects the shadow of the septa on the roentgenogram as a broad surface, giving the impression of a diffuse area of lung involvement. Stereo-roentgenograms do not bring out the true nature or location of this process. A lateral view, in the same plane as the interlobar fissure, affords a totally different conception of the limits of the process.

The authors qualify their interpretations of the roentgenograms published with the statement that all disease processes affecting these divisions of the lung would not occupy the areas designated in their diagrams: previous disease of the lung may have resulted in retraction, distortion, or displacement of the lung under consideration. The entire interlobar septum usually is not involved by the disease. Likewise, only a portion of one or more lobes may be affected. The general configuration of the affected parts, however, closely simulates the diagrams experimentally produced.

They point out that lung abscesses are most frequent in the superior division of the right lower lobe, and primary carcinoma of the lung infrequently occurs here. Pneumonia of the lower lobe is more frequent in

the superior division of the right side, and because of its central appearance on the roentgenogram is often called "central pneumonia." The physical signs of the process are found in a small circumscribed area posteriorly between the scapula and spine and between the fourth and eighth ribs.

Atelectasis, especially postoperative, is frequently found in the inferior division of the right lower lobe. Physical signs of atelectasis of this portion of the lung are frequently absent despite considerable involvement as seen on the roentgenogram. If atelectasis is of long duration, there is considerable diminution in size of the involved lung. The superior division of the lower lobe will become emphysematous and fill the posterior recess behind the diaphragm. Normal breath sounds and resonance are found posteriorly. Likewise, anteriorly the clear middle lobe will mask the involved lung. Dullness, if elicited, is continuous with the liver dullness.

It is interesting to note the infrequency of involvement of the entire left upper lobe by pneumonic consolidation, and the infrequency of effusion in the interlobar fissure. The left lower lobe was found to be as frequently involved by pneumonia as the right lower lobe. It also showed similar division of involvement in the superior and the inferior portion.

Physical signs of involvement of the interlobar fissure between the right upper and right lower lobe may be absent, because this fissure approaches the chest wall only in the axilla—its narrowest part. In the interlobar fissure between the right upper and right middle lobe the process is overlapped by considerable lung which, if not involved, cannot transmit the dullness of the effusion. An interlobar fissure completely surrounds the right upper lobe, a combination of that between the right upper and right lower lobes and the fissure between the right upper and right middle lobes. Because of the broad shadow obtained in the postero-anterior projection, which is less dense centrally near the hilus, involvement of these two fissures has often been misinterpreted as lung involvement and frequently as lung abscess. It is the posterior fissure, lying obliquely, which accounts for the broad shadow. The lateral projection clearly demonstrates the contour of this fissure.

Effusion between the middle and lower lobes is the most frequent of all interlobar effusions. The oblique course of this fissure explains the broad shadow seen in the roentgenogram in the postero-anterior projection.

Atelectatic lung is smaller than the normal lung. The middle lobe is a small lobe and when atelectatic may diminish so in size as to approach the dimensions of a large effusion between the lobes.

A high diaphragm superimposed over the cardiac shadow is frequently confused with an interlobar effusion between the middle and lower lobes. A superimposed pendulous breast may cast a shadow which can be erroneously interpreted as an interlobar effusion. The right interlobar fissure bordering the upper surface of the lower lobe is the major fissure separating the lobes. This fissure separates the lower lobe from the upper posteriorly (from the hilus to the posterior chest wall) and the lower lobe from the middle lobe anteriorly (from the hilus to the anterior chest wall). Effusion in this area can easily be mistaken

for a large tumor. A roentgenogram in the lateral projection clearly establishes the position of the shadow within the interlobar fissure. Interlobar effusions involving the fissure between the left upper and the left lower lobes are not common. Exudates in the interlobar fissures are by no means as infrequent as the paucity of reports in the literature would indicate. Stivelman[11] asserted that they cast shadows which are frequently misinterpreted. They may occur in any of the fissures; in one instance an exudate was found in the azygos fissure. In his experience, they account for many of the so-called mild and atypical pneumonic processes, and occasionally are confounded with intrathoracic neoplasms. Many cases of unresolved pneumonia, when not due to tuberculous processes, are either primary interlobar exudates or exudates complicating recently resolved pneumonic infections. Transudates secondary to circulatory failure may accumulate in interlobar fissures and closely simulate pulmonary consolidation or intrathoracic neoplasm. Clinically, an interlobar exudate may develop with so few constitutional disturbances and such moderate pain and cough that its accidental discovery on the roentgenogram may be disconcerting. As a rule, it makes its appearance in much less stormy fashion than lobar pneumonia, and while at times the cough may be quite distressing there is no bloody sputum. The paucity of physical findings in interlobar pleurisy is in itself of diagnostic importance. A critical drop in temperature is rarely observed in interlobar exudate, nor does the blood count show as high a leukocytic response and preponderance of neutrophils as it does in pneumonia. Interlobar exudates will rarely simulate endobronchial neoplasms with atelectasis of the tributary lung area, displacement of the trachea and mediastinal contents toward the involved side, narrowing of the interspaces and retraction of the diaphragm on the side of the lesion. In carcinoma with alveolar involvement, and in those casting a shadow in the hilum that extends toward the periphery, confusion with interlobar collections of fluid may occur. If roentgenograms in the lateral projection show these shadows to be intimately connected with an interlobar fissure, time and patience may be necessary to demonstrate the gradual disappearance of the shadow that will substantiate the interpretation of an interlobar exudate. The necessity of the postero-anterior and true lateral projection in the making of roentgenograms for studying of this type of lesion is stressed.

Baum[1] believed that electrosurgical severance of pleural adhesions may convert an ineffective artificial pneumothorax into an effective one. Since thoracoscopy is relatively harmless, intrapleural closed pneumolysis should be the treatment of choice in ineffective artificial pneumothorax. When adhesions become organized, forming fibrous strings, cords, bands, or fans, which prevent the tuberculous cavity from collapsing, or which, by contraction, cause a reëxpansion of the collapsed lung and reopening of the cavity, the aid of the roentgenologist may be invaluable. In questionable cases, the roentgenologist should not commit himself, because the roentgenographic picture differs frequently from the thoracoscopic. The final decision as to the procedure of intrapleural closed surgery should never be made on roentgenologic evidence alone.

In an effort to visualize intrapleural adhesions to decide which were

the chief factors in preventing proper collapse, or in holding open a cavity, Ellison[4] used oblique plane exposures of the hemothorax in which the pneumothorax existed. By using a lead screen covering half of the cassette (14″ by 17″) in the long diameter and changing the screen position between exposures, he juxtaposed one view made in an anterior oblique plane and one made in a posterior oblique plane on one film. This, with one roentgenogram made in the postero-anterior plane, gave him more information than he had in one set of roentgenograms made stereoscopically. The angle of rotation used to obtain the oblique views was about 45° from the plane of the film. In making the exposure in the posterior oblique position the forearm on the involved side was placed across the small of the back and in the anterior oblique position the arm was rotated inwards and the point of the shoulder was brought forward as far as possible. All exposures were made during the expiratory phase of respiration.

Encountering difficulty in the administration of gas to a patient in whom formerly there had been no difficulty, and whose fluoroscopic tracing showed a well collapsed lung, suggested to Blady and Cohen[2] the possibility of giving the treatment under fluoroscopic guidance. This was accomplished without difficulty with the aid of the fluoroscope. Since that time a weekly clinic at which difficult cases were treated under fluoroscopic guidance has proved of inestimable value and has produced gratifying results. The usual method is to observe the patient in the upright position, turning him until the suitable angle for the individual patient is determined. A direct tracing of the chest and the relative positions of the heart, trachea, hilar regions, diaphragm, and position and shape of the collapsed lung is made. The patient then lies down on the unaffected side and the affected side is fluoroscoped, using the horizontal ray. The findings are traced on a 14″ by 17″ celluloid transparency. From study of the two tracings the most suitable point for insertion of the needle is located. The needle is introduced under fluoroscopic control. All guess work in the difficult cases has been replaced by direct observation and accurate guidance.

Generalized pleural effusion accompanying congestive heart failure is observed frequently, but localized effusion with heart disease has not been emphasized. Shiflett[10] found records of localized interlobar effusions increasing as symptoms became severe and decreasing coincident with clinical improvement.

It is generally agreed by internists and pathologists that the lungs of the adult are relatively immune to syphilitic infection. There is ample pathologic evidence of the luetic etiology of the massive interstitial consolidation or white pneumonia of infants. Robinson[9] found reports of 12 cases from 2,800 autopsies at Johns Hopkins Hospital. Only 4 of these were in adults; 3 of the 12 had been recognized clinically. In 20,000 patients admitted to the Munster Clinic, Krause had observed only 5 cases. Roentgenologically, he found three types of lesions described: 1, Generalized thickening of all the bronchial markings, studded with minute "knobby" enlargements, radiating from the hilus into one or both lung fields and producing a characteristic fan-shaped effect, a diffuse interstitial fibrosis of the bronchial tree. Assmann described this lesion which, if bilateral, may be confused with the infil-

trative type of metastatic malignancy. If unilateral, it may simulate primary bronchogenic carcinoma of the infiltrating type. 2, Gumma of the lungs, which may be miliary and multiple or solitary, discrete masses several centimeters in diameter, appearing as nodular areas of increased density, usually near the hilus, or in the periphery of the lung field. In the early stages of development of these nodular areas a delimiting zone of pneumonitis is formed about them, this is replaced later by a fibrous connective-tissue capsule. Necrosis may present as an area of rarefaction in the central portion of the nodule, or fibrosis may occur. In the early stage of the solitary discrete mass, especially if it is situated in the periphery of the lung, the condition may be confused with lobular tuberculosis or abscess formation. In the later stage of encapsulation, when located near the hilus, it may simulate a primary malignant tumor. The miliary form may be erroneously interpreted as metastatic malignancy. 3, The diffuse lobar form, which is occasionally described as a clinical entity, is really a massive atelectasis secondary to bronchostenosis due to syphilis of the primary bronchus. Ordinarily, in uncomplicated syphilis of the lung, cavitation only occurs in the terminal stages, and then as a result of bronchial dilatation and bronchiectasis. Calcification has never been noted in syphilis of the lung. There are no pathognomonic roentgenographic images of syphilis of the lung. Various observers have credited the lesion with a predilection for the middle lobe of the right lung, the hilar zone in one lung field, or the base of one lung. Symptoms and signs are quite variable, usually dependent on the nature and extent of the lesion; they may even be absent. They may be manifested by a dry, trivial cough or the expectoration of a mucopurulent sputum, with febrile reaction and all signs of an active tuberculosis. A sudden and severe hemoptysis may be the first symptom. In a case of syphilitic tuberculous symbiosis, with sputum showing positive findings of tubercle bacilli, an associated syphilis of the lung would never be suspected. Many cases are probably missed or confused with tuberculosis or tumor of the lung, which may account in part for the rarity of the disease. The case he reported was in a negress, aged 36, which conformed to all the criteria laid down for a diagnosis of syphilis of the lung, namely, syphilitic history, signs and symptoms of a chronic, stubborn, progressive pulmonary lesion, repeated examinations with failure to find tubercle bacilli in the sputum, positive serology and a lesion which roentgenographically was more extensive than the physical condition of the patient warranted. Response to specific therapy was prompt and lasting. Wigby and Sanders[13] reported a case of gumma of the lung in a negro, aged 34, with surrounding syphilitic pneumonia which was found at necropsy.

Fruchter,[5] in discussing discrete pulmonary lesions, presented a type of pulmonary tuberculosis to which Abbert, Fraenkel and Straub recently called attention occurring as isolated, sharply defined, coin-sized, round encapsulated shadows with no reaction in the surrounding tissues. These may develop with or without fever and with positive or negative findings in the sputum examinations. The foci may remain stationary for years, even in the presence of a progressive and finally fatal tuberculosis elsewhere. They may eventually progress, however, and go on to liquefaction and cavitation, extending into the surrounding

tissue by the formation of daughter foci. These lesions constitute a rare form of exudative focal tuberculous inflammation isolated by a connective tissue capsule. One has difficulty in differentiating these lesions from tumor metastases, which commonly appear as discrete pulmonary shadows. They may simulate non-tuberculous bronchopneumonia, syphiloma, cysticercosis, and echinococcus cysts. The clinical history has a prominent place in making the differential diagnosis. Repeated or serial roentgenograms to study the morphologic changes are all but indispensable.

Pulmonary calcifications interested Aristotle and since his time have fascinated the minds of generations of medical investigators. Pendergrass and de Lorimier[7] stated that the biogenetic nature of their development is not known. Wells, after an exhaustive study, concluded that there seemed to be no essential differences between the processes involved in normal ossification and in most instances that of pathologic calcification; any area of calcification may be changed to true bone in the course of time. In general, when one attempts to account for calcified lesions in the lungs, these four possibilities are to be considered: 1, Secondary calcification after degeneration or necrosis due to infection; 2, primary or secondary calcification of aspirated foreign bodies; 3, precipitation of the osseous inorganic elements, due to excessive concentration of these in the blood; and 4, metastases of bone-forming cells. Concretions of grossly visible dimensions, produced by any of these four general types of processes, are spoken of as "pneumoliths," "lung calculi" or "lung stones." When parenchymal concretions erode through the walls of the bronchi and become free in the lumina of the bronchi or bronchioles, the term "broncholith" is applied. These broncholiths are irritating to the mucosa, a cough reflex is stimulated and with cough a change in the position of the broncholith occurs with further irritation. Bronchorrhea (excessive secretion of mucus) and bronchial colic (bronchial spasm) with wheezing and expiratory dyspnea are the underlying causes of a symptomatology often described as "stone asthma." Paroxysmal cough is the rule, sometimes climaxed by an explosive effort which usually results in expelling a stone or gritty material. Pain, tearing or cutting, localized to the poststernal region or referred to one or the other lateral portion of the chest results from the cough paroxysms. Hemoptysis usually occurs with the passage of a stone; it may occur repeatedly during the coughing attacks, or occur periodically over several weeks or months. Many of these cases are considered to be pulmonary tuberculosis, notwithstanding repeated negative examinations of sputum. If secondary infections occur the condition becomes masked by the symptoms and signs of chronic bronchitis, bronchiectasis, abscess or pneumonia. Roentgenologic examination and recognition of the concretion, occasionally exhibiting a peripheral wedge-shaped area of atelectasis or dense infiltration, and subsequent bronchoscopic removal of the concretion offers a favorable prognosis in an otherwise puzzling and distressing malady.

Congenital cystic lung is a rare anomaly. The few cases surviving infancy offer interesting studies. The literature is filled with conflicting terms for the same congenital anomaly, congenital bronchiectasis, congenital cystic lung, atelectatic bronchiectasis, honey-comb lung. The various terms probably have arisen in association with the many theo-

ries of origin. A congenital origin seems the most plausible, and most easily explains the great number of cystic lungs found in still births and young infants. Congenital cardiac and skeletal lesions are frequent accompaniments. Cysts encountered in adults are usually altered by infection and their origin is difficult to determine, but Koontz noted that a lack of pigment in the tissue involved showed that the part never functioned and is evidence again that the condition antedated birth. Most writers agree on a congenital origin, but its cause is altogether obscure. As to cysts, there are two types reported, the large solitary and the small multiple. The terms above would seem to apply more aptly to the multiple. The two types seem closely related and probably both have a similar congenital origin. The two have occurred together in the same patient, and are probably merely a different expression of the same condition. Some contain fluid when first noticed; in one large solitary cyst of the left lower lobe reported in an infant, the fluid was spontaneously coughed up and the cyst became filled with air. Multiple cysts similarly at first may contain fluid, the fluid later being replaced by air when bronchial communication occurs during development and growth of the lung.

Recognition of the larger solitary cysts is not difficult in the face of severe symptoms. Recurrent attacks of dyspnea and cyanosis in an infant with hyperresonance and displacement of the mediastinum should suggest a cyst rapidly filling with air. Roentgenologic examination should confirm the diagnosis, either alone or with the aid of lipiodol. Small multiple cysts are less easily picked up and, if no infection supervenes, may remain silent in the adult, when diagnosis is unimportant. Infection in infants simulates bronchiectasis with cough and sepsis. There may be little or no sputum. Prognosis is poor, and death ensues usually within the first few weeks or months following birth. Thorpe[12] presented a 10-year record of the small multiple cyst type, a chance Roentgen finding in a routine school examination in which investigation revealed previous roentgenographic examination in infancy. At that time there was infection with cough and fever and the diagnosis was congenital bronchiectasis. The case is remarkable from the fact that the involvement was in an accessory lobe. The patient, a Japanese girl, aged 13, was referred for a Roengen examination of the chest. The clinical diagnosis was tuberculosis. Her complaint was a mild chronic non-productive cough and underweight. In the 10 years since she was first examined she had an intermittent dry cough, her history showed she had spasms of cough without sputum at the age of 2 years, and an attack of whooping cough shortly after birth suggested early manifestation of an anomaly. A roentgenogram of the chest revealed the same multiple air-containing cysts in the right lower lobe noted in March, 1924. They occupied a triangle medially and opposite the heart laterally, so that the normal lung surrounded the cystic area. Their lateral limit was a straight sharp line with slight tenting at its junction with the diaphragm. The heart was not displaced. Roentgenoscopy revealed a slight lag of the diaphragm on the right. Cough elicited no noticeable winking of the cysts.

Reitter[8] presented a case of a white girl, aged 9, whose mother stated that the child had always had some cough, productive at times. The child was referred with a clinical diagnosis of pulmonary tuberculosis, and never had whooping cough, pneumonia or any other acute respira-

tory infection. Physical examination showed clubbing of the fingers and marked pulmonary osteoarthropathy. Roentgenographic examination showed multiple globular cavitations throughout both lungs, with considerable infiltration along the bronchi. Eight Mantoux tests were all negative. Postural drainage produced greenish-mucopurulent sputum on only one occasion tinged with blood. The diagnosis was congenital bronchiectasis.

Acute influenza pneumonitis was applied by Bowen[3] as a term to designate infiltrations localized in various portions of the lung observed in routine Roentgen examinations of patients with mild cases of influenza in the military hospitals in Hawaii. The interesting feature of his roentgenographic reproductions is the simulation of numerous types of lesion including bronchiectasis, abscess, primary and metastastic malignancy. Resolution was the rule in from 7 to 10 days. The typical patient recovered in a few days but routine roentgenographic chest examination revealed a very high incidence of this localized involvement.

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PHYSIOLOGY

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Correlated Morphological and Regional Differences in Brain Cultures.—S. CULVER WILLIAMS (Laboratory of Anatomy, University of Pennsylvania). Tissue cultures in hanging drops of diluted chicken

plasma-embryonic extract were made from mapped regions of the hind-brain of 5-day incubated chick embryos. A study of over a thousand such cultures from 86 brains showed that three regions in each half of the medulla were distinguishable by the character of their behavior.

That part of the medulla anterior to the level of exit of the fifth cranial nerve gave cultures from which for 5 days the outgrowing nerve fibers were relatively straight, moderately branched, and with most branches diverging from one another at a small angle. This region comprises a thick basal plate and a thinner alar plate. Cultures from the basal plate usually show a thining of the explant which exposes structures within it, while from the alar plate, cultures are less apt to thin out.

Cultures from the medulla behind the region of exit of the seventh cranial nerve more frequently show winding highly branched fibers, with many branches diverging widely from one another.

Assuming the culture medium to be the same for all cultures, such differences in morphology may be due to inherent conditions that differ in regional distribution within the brain, for the possibility of external influences from normal growing tracts of fibers nearby has been eliminated.

Some of the differences noted may be ascribed to the behavior of the ameboid growth cone at the active tip of the extending fiber, which is apparently a particularly sensitive portion of the cell surface. Some differences may be related to the fact that the basal plate includes many motor cells, while in the alar plate are many sensory cells.

Whatever the inherent factors responsible, enough are retained under cultural conditions to give recognizable morphological distinctions.

Further Studies on the Effect of Section of One Peroneal Nerve of the Albino Rat on the Intact Nerve of the Opposite Side.—Kozo Tamaki (Wistar Institute, University of Pennsylvania). In a previous study (1933), it was found that section of one peroneal nerve in the albino rat arrested the formation of myelinated fibers in the contralateral nerve, sometimes causing even a loss.

The present study was made to determine how the age of the rat at operation or the prolongation of the interval between operation and killing affected the results.

It was found that the number of myelinated fibers in the tests was always less than in the corresponding controls. With the advancing age at operation, this effect became more marked, while with the increase of the interval after operation, it diminished, thus indicating recovery.

The increases in the sectional areas of the entire nerve were also recorded. The same relations as for the number of fibers were found for the areas.

Thus section of the peroneal nerve on one side of the rat modifies the constitution and the area of the contralateral nerve; but this reaction is in turn modified by the age of the rat at operation and by the length of the postoperative interval. These effects are considered as brought about by toxic substances formed by the damaged neurons, and acting on the corresponding neurons in the opposite side of the cord.

A Convenient Method for the Determination of the Approximate Cardiac Output in Man.—JOHN S. DONAL, JR. (Laboratory of Pharmacology, University of Pennsylvania). The purpose of this investigation was to design a cardiac output method more simple than any now in use, and to test its accuracy by comparison with more complicated procedures.

Previous investigators have estimated the oxygen content of the venous blood in man by attempting to secure complete equilibrium between the blood and lung air. The unavoidable dilution of any rebreathed mixture by the residual air makes this process difficult and uncertain and the numerous analyses involved are time-consuming. A method has therefore been developed in which approximate equilibrium with the venous blood is attained in a single rebreathing of about 2500 cc. of nitrogen. Two accurately timed samples, taken after mixing is complete and before recirculation begins, permit the calculation of the cardiac output from the formula:

$$\text{Cardiac output} = \frac{(A-B)}{(C-D)}$$

where A is the oxygen consumption in cc. per minute, measured in the usual manner; B is the oxygen consumption in cc. per minute during the rebreathing period between the collection of samples; C is the normal arterial oxygen content, or 96% of the blood oxygen capacity, as estimated from a hemoglobin determination; and D is the oxygen content of arterial blood as calculated from the average of the tensions of oxygen and carbon dioxid in the two alveolar samples and a standard nomogram.

The oxygen consumption, B, found during the rebreathing of nitrogen, is calculated from an assumed volume of residual air which is not accurately estimated. It should also be corrected for the unknown change in circulatory rate resulting from rebreathing. B is small compared to A, however, and it has been found that these errors do not greatly affect the calculated cardiac output.

Estimations of basal cardiac output by this procedure have been found to be in good agreement with determinations made on the same subjects by the ethyl iodid method of Starr and Gamble and by the acetylene method of Grollman.

A Circulation Schema, with Pumps Obeying Starling's "Law of the Heart."—*I. The Construction of the Schema from Physiological Data. II. On the Causes of Increased Venous Pressure, in the Schema, and in Certain Clinical Conditions.* ISAAC STARR, JR., and A. J. RAWSON (Department of Research Therapeutics and Johnson Foundation, University of Pennsylvania). A circulation schema has been constructed, with pumps which fill without suction and put forth more work the more completely they are filled; *i. e.*, their behavior simulates Starling's Law of the Heart. In this schema the factors responsible for increases of venous pressure as the "heart" is weakened can be divided into two main classes by their relationship to the general systemic pressure, *i. e.*, the pressure existing throughout the system when the pump is stopped. Thus if increased "venous" pressure is caused by appropriate alteration of the resistances, or by weakening one side of the heart, venous pressure falls when the heart is stopped. If increased

venous pressure is due to a diminution of the reduction of pressure, which can be demonstrated on the "venous" side of any circulation when a single pump is started, the venous pressure will rise when the pump is stopped. If an increased venous pressure is due to an elevation of the general systemic pressure, the venous pressure remains elevated after the pump is stopped.

The reduction in cardiac output following weakening of the "heart" can be compensated by increasing the general systemic pressure in our schema.

In the clinic, we have attempted to analyze the factors causing increased venous pressure by comparing this pressure during life with the pressure prevailing throughout the circulation immediately after the cessation of cardiac action. The latter pressure remains very constant for at least 1 hour after death. Ten cases never known to have had increased venous pressure during life had general systemic pressures, ranging from 11 to 0, average 4.6 cm. H_2O after cessation of cardiac action. Cases with increased venous pressure during life divide themselves into two classes. For example, in a man with venous obstruction, the pressure fell from 50 cm. during life to 4 cm. after death. But in several cardiac cases the increased venous pressure was maintained after death at a point very close to its level during life.

The results suggest that these cardiac cases had an increased general systemic pressure, perhaps to compensate for cardiac weakness, and that this is an important factor in the increased venous pressure they exhibited during life.

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ORIGINAL ARTICLES.

THE INTERRELATIONSHIPS OF THE GLANDS OF INTERNAL SECRETION CONCERNED WITH METABOLISM.*

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(From the George S. Cox Medical Research Institute, University of Pennsylvania.)

The title of this lecture embodies three questions. One is, what do we mean by metabolism; secondly, what is the manner in which the hormones influence metabolism; and lastly, do the endocrine glands, by their various secretions, alter the activity of other glands which in turn must lead to deviations in the metabolic processes?

It is obvious at the present time that any attempt to understand these questions fully is impossible. We are not only ignorant of the majority of the finer metabolic changes, but our knowledge of the essential activity of any hormone is very incomplete. Finally, when we attempt to explain the manner in which the activity of one endocrine gland influences that of another, we only too often find ourselves indulging our imagination under the guise of scientific truth.

Nevertheless, I shall attempt to lay before you certain phases of metabolism with which we know the glands of internal secretion to be particularly concerned, and to show how more recent work is beginning to give us some insight into the true nature of glandular interrelationships.

Before proceeding to any discussion of these interrelationships

* The Thirty-fifth Mary Scott Newbold Lecture of the College of Physicians, Philadelphia, delivered October 2, 1935.

it would be as well to refresh our memory on what we mean by metabolism. By this word we signify the sum total of chemical changes which occur in the organism. These changes involve not only oxidation and reduction, but also the synthesis and degradation of a large number of chemical compounds.

The Metabolic Process Considered. It will be impossible to discuss more than a few of these transformations and, furthermore, I intend to limit my remarks to certain changes involving proteins, fats and carbohydrates. The equally important mineral metabolism of the body will have to be largely neglected, partly owing to lack of time, but chiefly owing to the fact that our knowledge of these phases of metabolism is even more incomplete than it is in the case of the above substances.

The most important metabolic changes involving the proteins, fats and carbohydrates are as follows:

A. Carbohydrates of the food or derived from body stores are delivered to the tissues in the form of glucose.

B. Proteins, whether derived from food or mobilized from tissue reserves are converted into amino acids. About one-half of these amino acids are deaminated and converted into glucose in the liver. The remainder are also deaminated, but then probably follow the same metabolic pathway as the fatty acids. Finally, a certain amount of resynthesis of body protein is also carried out from amino acids.

C. The fats are split into fatty acids and glycerol. The latter substance is, we believe, converted into glucose, while the fatty acids are oxidized to CO_2 and H_2O.

While it is not impossible that protein may be metabolized without following the path of glucose or fatty acids, for the purpose of our argument we will assume that this is unusual.

This interconversion of foodstuffs is further completed by the fact that glucose may, under certain circumstances, be converted into fatty acids. The reverse change, the conversion of fat to carbohydrate, although postulated by some authorities, is at present not accepted by the majority of workers in this field.

We have in this manner reduced our study of the metabolism of protein, fat and carbohydrate largely to a consideration of the production of glucose and its utilization, and to the metabolism of fatty acids.

When a certain quantity of glucose, whatever its source, is presented to the tissues, we know that two main transformations result: *a*, a certain portion is oxidized to CO_2 and H_2O; *b*, another portion is converted into glycogen. Part of this glycogen is stored in the liver while a somewhat larger portion appears in the muscles. The liver glycogen is usually held to be simply storage carbohydrate, but there is no doubt that the muscle glycogen is intimately concerned with contraction and follows a different metabolic pathway.

It should be noted that some workers have held the view that a preliminary transformation of glucose to glycogen is a necessary step in its oxidation.

The manner in which the long carbon chains of the fatty acids are reduced to CO_2 and H_2O has been the subject of many brilliant researches by Knopp. This worker has evolved the following scheme: *a*, the beta carbon atom (*i. e.*, the second carbon atom from the carboxyl group) is the point at which oxidation occurs. This removes two carbon atoms from the chain. *b*, this successive lopping off of two carbon atoms finally results in a four-carbon ketoxy or hydroxy acid, *i. e.*, acetoacetic acid or betahydroxybutyric acid. Further oxidation of these acids results in the formation of CO_2 and water.

Now it is around this last stage of fat oxidation, that is of the acetone bodies, acetoacetic acid and betahydroxybutyric acid, that some of the most interesting work in metabolism has been done. Shaffer, from *in vitro* experiments, concluded that for the complete oxidation of the acetone bodies a certain proportion of glucose oxidation is necessary. This has apparently been substantiated for the whole organism by many investigators, and in the hands of Woodyatt and others has formed the basis for the explanation of certain phenomena observed in pancreatic diabetes.

The coupling up of the final stages of carbohydrate and fat metabolism is one of the most interesting and difficult problems of metabolism, particularly since more recent work has tended to cast some doubt upon the whole concept.

We have very briefly outlined some of the major phases of the metabolism of protein, fat and carbohydrate and we now have to consider in what manner these changes are influenced or diverted by the various hormones.

Hormones as Catalysts. The many chemical changes that occur during metabolism take place under practically isothermal conditions. This is rendered possible by the presence in the body of substances which may be grouped under the general term of catalysts.

These biologic catalysts can be divided roughly into four groups:

A. The digestive enzymes such as pepsin and trypsin.

B. The intra- and extracellular enzymes and catalysts, such as arginase, phosphatase and glutathione.

C. The vitamins.

D. The hormones.

In the case of the last two groups, the vitamins and hormones, it has not been definitely established that they bring about their effects by catalytic action, but nevertheless, in the case of ascorbic acid and insulin the evidence at present is highly suggestive that this is the manner in which they participate in the body economy. A further difference of these substances from those in the first

two groups is that they require the presence of intact, living cells for the demonstration of the activity.

Without pressing the analogy between hormones and catalysts too far, it is my intention to outline the effects of certain hormones upon metabolic processes as though these chemical reactions were markedly accelerated or retarded by these substances in the manner in which well defined catalysts have been shown to influence other chemical changes.

The Hormones Influencing Glucose and Fatty Acid Metabolism. In investigating the function of any hormone three methods are usually followed:

A. Study of the effects of complete deprivation by excision of the glands secreting the particular hormone.

B. Study of the effects produced by replacement of the excised gland by a purified preparation of the hormone.

C. Study of the effects produced in a normal animal by the injection of such a purified preparation.

By the use of these methods the following hormones have been demonstrated to exert a marked influence on glucose and fatty acid metabolism.

I. **Epinephrin.** *A.* Removal of all adrenal medullary tissue renders the animal sensitive to insulin, and unable to counteract successfully the effects of exposure to cold by an increased heat production. In addition many of the usual phenomena invoked by pain or emotion are absent. From our point of view, the most interesting effect is the failure of the blood sugar to increase under these conditions.

B. An injection of epinephrin produces the following changes in carbohydrate metabolism: 1, The blood sugar rises and glycosuria may appear; 2, the blood lactic acid increases; 3, the liver glycogen at first is decreased and then increased; 4, the muscle glycogen is converted into lactic acid which is carried to the liver and converted into glycogen. As a result the liver glycogen is finally increased above its initial level; 5, glucose utilization in the tissues is decreased.

Thus under the influence of epinephrin a cycle of the formed carbohydrate elements of the body is established. In other words this hormone effects a redistribution of the carbohydrate of the body by increasing the rate of glycogenolysis both in muscle and liver. It is important to recognize that epinephrin does not stimulate the formation of new carbohydrate from protein, nor can it produce a true diabetes mellitus in an intact animal. In this sense, epinephrin is not a contra-insulin or diabetogenic hormone.

II. **Thyroxin.** *A.* It is well known that total thyroidectomy results in a marked fall in oxygen consumption. It is not so well known that completely thyroidectomized animals exhibit but slight blood sugar responses to epinephrin injection.

B. The injection of thyroxin into normal animals produces a marked increase in oxygen consumption and a depletion of the body stores of glycogen.

The effect of epinephrin upon the blood sugar of animals treated with thyroxin is dependent upon the liver glycogen stores. Thus, so long as liver glycogen is present epinephrin hyperglycemia is exaggerated. When, however, the liver glycogen has been depleted epinephrin has but little effect upon the blood sugar. This apparent interrelationship between the thyroid and adrenal medulla is therefore largely determined by the quantity of liver glycogen present. It is probable, however, that one of the effects of thyroxin is to sensitize the sympathetic nerve endings so that minimal amounts of epinephrin produce very large effects.

In a similar manner there is an apparent relationship between insulin and the thyroid hormone which upon examination is also more reasonably interpreted in terms of the liver glycogen content. Thus small doses of thyroid extract diminish the hypoglycemic action of insulin so long as liver glycogen is present. However, when liver glycogen has been depleted by prolonged thyroid influence, the injection of minimal amounts of insulin will precipitate a fatal hypoglycemia.

It is apparent that, depending upon the condition of the liver glycogen stores when the experiments were made, we might in some cases be led to assume that an antagonistic relationship existed between the thyroid or the adrenal and the pancreas, while in others that the hormones were reinforcing each other. As a matter of fact, what is probably happening is that each hormone is exerting its action independently of the other. The response obtained is determined by the existing conditions and not by the presence or absence of another hormone.

I have dealt at some length with these supposed thyroid, adrenal medulla, pancreas relationships since they have played a not inconsiderable part in the history of diabetes mellitus. The concept was first introduced by Falta, Eppinger and Rudinger, and rapidly became associated with the so-called overproduction hypothesis of diabetes mellitus.

III. **Cortin.** *A.* Complete removal of all adrenal cortical tissue is followed by a condition characterized by loss of sodium from the body, hemoconcentration and death. Very frequently such adrenalectomized animals develop marked hypoglycemia, and usually have depleted liver glycogen stores. Until recently it has been assumed that this hypoglycemia and carbohydrate depletion was a result of the disturbance in the water and salt metabolism, although why this should occur as a result of hemoconcentration has always been difficult to answer. In traumatic shock, for instance, where equally great hemoconcentration is present, the blood sugar is usually increased.

A recent publication by Harrop and his co-workers[1] has done much to clarify the occurrence of hypoglycemia following adrenalectomy. They have found that even if dogs were adequately maintained by cortical extracts or salt feeding they still developed hypoglycemia upon fasting. This indicates that under these conditions the adrenalectomized animal is unable to maintain his blood sugar; in other words, although the salt and water metabolism has been restored to normal, there still exists a defect in the carbohydrate metabolism. The importance of this observation will be more apparent when we discuss the effects of adrenalectomy upon pancreatic diabetes. Up to the present the injection into normal animals of large amounts of a cortical extract capable of maintaining adrenalectomized animals has not been followed by any recognizable changes in metabolism.

IV. **Insulin.** When we consider the effects of total insulin deprivation we are of course at once confronted with the problems of clinical and experimental diabetes mellitus. The sequence of events following total deprivation of insulin are as follows: 1, Hyperglycemia and glycosuria that persist during fasting. 2, An increased nitrogen excretion and the development of a constant proportion between the urinary glucose and nitrogen. This proportion, usually spoken of as the G/N or D/N ratio, is one of the most characteristic features of a total diabetes. It has been interpreted, chiefly by the work of Lusk, to indicate that a constant proportion of the amino acids either from the food or body proteins is converted into glucose. Since, 3, it has been held that glucose oxidation virtually ceases in the absence of insulin, all such glucose formed from amino acids is excreted. 4, Finally, large quantities of the acetone bodies betahydroxbutyric acid and acetoacetic acid appear in the urine.

These facts are well established. It is upon the interpretation of the manner in which these various phenomena are brought about that a wide difference of opinion has arisen. Until recently it has been generally accepted that the increased metabolism of protein and fat was a direct consequence of the endeavors of the organism to meet its metabolic demands in the absence of glucose utilization. This point of view looks upon the failure of glucose oxidation in the absence of insulin as the essential defect. The other metabolic changes follow as an attempt at compensation.

Another group of workers has held a different view. The originators of this theory were Falta, Eppinger and Rudinger and their explanation has come to be spoken of as the "overproduction theory." This group has held that there exists an interrelationship between the thyroid, adrenal medulla and the islands of Langerhans. When insulin is removed a glandular imbalance is established. As a result the activity of the adrenal medulla and the thyroid markedly increases the production of glucose from protein and fat. As a

consequence the body is flooded with glucose and the products of fat metabolism—the acetone bodies. This school has also maintained that the normal capacity of the tissues to utilize carbohydrates persists, but the large amounts of glucose presented to them as a result of the overproduction mechanisms overtax their capacity of utilization and hyperglycemia and glycosuria occur.

Without going into details it may be stated that this original theory has been unacceptable to the great majority of physiologists. In the first place, as I have already indicated, it is unlikely that any such glandular interrelationship exists, and secondly, the view that fatty acids may be converted into glucose is without support.

Nevertheless, this "overproduction hypothesis" has introduced the concept of a glandular imbalance as playing a part in the diabetic syndrome as opposed to the view that hypofunction of the pancreas alone invokes these marked metabolic disturbances, without altering the activity of the other endocrine glands concerned with metabolism.

With these ideas concerning diabetes mellitus before us, let us pass to the consideration of another endocrine gland which until recently had been very much neglected from the point of view of its possible metabolic effects. I refer, of course, to the anterior pituitary. As before, let us first consider the effects of removal of the hormones of this endocrine gland upon the organism.

V. **Anterior Pituitary.** Following hypophysectomy in mammals, birds, amphibia, reptiles and fish, there occurs a most striking atrophy of practically all the endocrine organs. Those most markedly involved are the gonads, thyroid, adrenal cortex and, to a lesser extent, the parathyroids and thymus. It is also probable that the islands of Langerhans are involved in this atrophy, but their anatomic situation makes this rather difficult to decide. One fact to be remembered is that the adrenal medulla, so far as one can judge, is not involved.

In view of these findings it is not remarkable that hypophysectomy results in marked metabolic disturbances. Those reported up to the present are:

A. A decreased metabolic rate and cessation of growth.

B. A lowered blood sugar and the development of hypoglycemia symptoms on fasting.

C. A marked sensitivity towards insulin.

D. A decreased response of the blood sugar to epinephrin injections (Cope and Marks),[2] *i. e.*, resistance to this hormone.

E. A decreased fasting nitrogen excretion (Braier).[3]

F. When glucose is fed a large part of it is unaccounted for in terms of glucose oxidation or glycogen storage (Phillips and Robb).[4]

G. In some animals markedly increased fat deposition (Cope and Marks).[2]

H. An atypical response to phloridzin characterized by decreased glucose, nitrogen and acetone body excretion (Houssay).[5]

It is apparent from a study of this table that in addition to the anatomic changes in the endocrines widespread metabolic disturbances involving protein, fat and carbohydrate are produced by removal of the anterior pituitary. This is suggestive of an equally close functional interrelationship between the anterior pituitary and the various endocrines enumerated above.

The dominant influence of the anterior pituitary is further emphasized by the study of the effects of anterior pituitary extracts injected into hypophysectomized and normal animals. Thus the injection of crude alkalin extracts has been shown to cause both anatomic and physiologic restoration of the gonads, adrenal cortex and thyroid as well as a resumption of growth.

When these crude extracts are injected into normal animals the metabolic rate is increased while at the same time the thyroid becomes hyperplastic. Another striking effect is the development of resistance to insulin.

Houssay[6] has reported that the continued injection of such extracts in normal fed dogs leads in a few days to marked hyperglycemia and glycosuria. In this he is supported by Evans, Bauman and Marine and others. For my own part, up to the present, I have not seen either crude or purified anterior pituitary extracts produce these effects in normal animals and other workers have reported similar negative results. The production of diabetes mellitus in normal animals by anterior pituitary injections is only one of the many important problems that awaits future investigation.

Considerable progress has been made in the fractionation of anterior pituitary extracts by Collip and his co-workers.[7] The following fractions have been obtained: *A*, Growth (+ glycosuric in suitable preparations); *B*, thyrotropic (+ ketogenic) — repair of thyroid in hypophysectomized animals; *C*, adrenotropic (practically free from all others); *D*, gonadotropic. Other effects of pituitary extracts are reported, but so far without extensive purification: *A*, Lactation factor; *B*, parathyrotropic; *C*, pancreatotropic—stimulates islands of Langerhans.

It is not my purpose to comment on the apparent paradox of the presence of this large number of apparently specific hormones in an organ that only contains three distinct types of cells. It is probable, however, that further work will reduce rather than increase the number of these hormones as we gain knowledge not only of their chemical nature, but also of their exact physiologic properties.

There is, however, one feature of the majority of anterior pituitary

hormones that is particularly important. This is the trophic nature of their action. By this we mean that in the case of the hormones affecting the gonads, thyroid, adrenal cortex, it has been abundantly demonstrated that they are without physiologic effect if the gonads, thyroid or adrenals are removed. In other words, they produce their effects upon the organism by stimulating the particular endocrine to pour forth larger amounts of its secretion. Thus the thyrotropic hormone not only causes hyperplasia of the thyroid, but also a condition of hyperthyroidism as a result of the increased amount of thyroid secretion that is liberated into the blood stream. Conversely, removal of the anterior pituitary produces a condition largely due to simultaneous hypofunction of nearly all the endocrine organs. The dominant control of the anterior pituitary over the other glands of internal secretion is probably the most important finding in endocrinology in recent years.

The Anterior Pituitary and Pancreatic Diabetes. We have already noted some alterations in the carbohydrate metabolism of hypophysectomized animals. These are: *a*, the occurrence of hypoglycemia on fasting; *b*, an increased sensitivity to insulin; *c*, an abnormal disposal of ingested carbohydrate. In addition I have suggested to you the concept that in another condition characterized by a markedly abnormal carbohydrate metabolism, to wit, diabetes mellitus, glandular interrelationships may play a part.

It has remained for Houssay and his co-workers to discover the beautiful but intricate relationship between the anterior pituitary and the pancreas as is shown by their effects upon carbohydrate metabolism.

About 1927 Houssay and his associates[8] began the publication of a long series of papers concerning the effects of a previous hypophysectomy upon the diabetes following total extirpation of the pancreas. The first experiments were carried out upon toads; they were however rapidly extended to dogs. The findings in both species were as follows: 1, after pancreatectomy in an hypophysectomized animal the degree of hyperglycemia and glycosuria was much diminished compared with that following pancreatectomy in an intact animal; 2, the nitrogen excretion and the dextrose-nitrogen ratio in the urine were also decreased; 3, ketonuria was markedly reduced and diabetic acidosis and coma did not occur; 4, as a consequence of these changes the animals survived for a long period. The diabetes was not entirely obliterated, but was transformed from a rapidly fatal condition into one of mild degree. Thus dogs which ordinarily only live about 2 weeks after pancreatectomy survived for 6 months or more if the hypophysis were also removed; 5, these animals doubly operated upon were extremely liable to hypoglycemic episodes, especially if fasted—glucose injections being often necessary to save their lives; 6, the carbohydrate tolerance, although not normal, was often greatly superior to that of the control depan-

creatized group; 7, marked loss of weight occurred in all those doubly operated upon that survived long periods and, in fact, these animals ultimately succumbed to inanition. This loss of weight is in part to be attributed to the absence of the external pancreatic secretion and partly to the mild diabetic state that persists; 8, removal of the thyroid before pancreatectomy did not alleviate the diabetes.

In the first experiments upon toads, Houssay[9] was able to show that implantation of the anterior lobe of the pituitary brought about a return of the diabetes to its usual severity. Similar experiments in dogs were at first unsuccessful; but in more recent work with alkalin extracts of bovine anterior pituitaries, Houssay was able to exaggerate markedly the diabetic state of his doubly operated dogs, as evidenced by the increased excretion of glucose and acetone bodies.

These remarkable results have been confirmed by several workers upon the dog, while Lukens and I[10] have shown that an equally large amelioration is observed in the severe diabetes that occurs in cats following pancreatectomy.

It will also be realized that these findings point to a participation of the anterior pituitary gland in the metabolic disturbances following pancreatectomy. In other words the "overproduction hypothesis" of diabetes mellitus receives some confirmation. Too much credit should not be given to the original exponents of this view, since: *a*, it is the anterior pituitary and not the adrenal and thyroid that are antagonistic to the pancreas; *b*, as we shall see, carbohydrate utilization is not greatly improved by hypophysectomy and *c*, there is still no decisive evidence that fatty acids can form glucose.

During the last 2 years Dr. Lukens and I have been carrying out experiments upon the mechanisms by which hypophysectomy produces its effects upon an experimental diabetes.

It has been our opinion that the best method to employ would be to study one species of animal and by the use of a sufficient number determine what was the usual response to a total pancreatectomy. We have also made observations upon a number of factors involved in the diabetic syndrome, that is, upon *a*, survival, *b*, degree of hyperglycemia and glycosuria under fasting and fed conditions, *c*, development and degree of ketonuria, *d*, clinical course and mode of death. In this manner we arrive at a standard against which the effects of any procedure upon experimental diabetes can be judged.

We have received ample confirmation that hypophysectomy not only increases the survival of depancreatized cats, but also results in a markedly lower glucose, nitrogen and ketone excretion under fasting conditions. Since acidosis and ketosis do not occur in such animals the increased survival must be largely due to the removal

of factors that normally precipitate them. It should be emphasized that the diabetic state is not completely remedied by hypophysectomy. In the cat particularly it is merely transformed from one of great severity accompanied by intense ketonuria to one of mild degree without ketonuria.

As we have already mentioned, the final stages of fatty acid metabolism are held to be intimately coupled with the oxidation of a certain proportion of glucose. Furthermore, another apparently well grounded hypothesis is that in the absence of insulin glucose oxidation is virtually absent.

In the case of the hypophysectomized and depancreatized animal two questions arise, either of which challenges one or the other of the above concepts. *A*, Is the disappearance of ketonuria due to the resumption of sufficient carbohydrate utilization to complete these final stages of fatty acid metabolism; or *B*, in the absence of the hypophysis is the metabolism of fatty acids completed even though the amount of carbohydrate oxidation is not altered?

If the removal of the hypophysis allows the amount of carbohydrate oxidation to increase, then the view that the sole defect in diabetes mellitus is failure of carbohydrate oxidation is placed in jeopardy. On the other hand, if carbohydrate oxidation is not improved by hypophysectomy then the view of the necessity of the coupling of this process with acetone body utilization is one that applies only under a definite set of conditions.

We have therefore carried out a number of experiments to determine to what extent carbohydrate utilization is improved by hypophysectomy.

In the first group we gave 3 gm. of glucose intraperitoneally to hypophysectomized-depancreatized cats and found that this was followed by a typically diabetic response of the blood sugar.*

In the next experiments we placed the animals on a constant diet and after a suitable fore period added 6 gm. of glucose to the diet. The recovery of the added glucose was quantitative, exactly as it is in the totally depancreatized animal.

Finally we placed the animals on a protein-fat diet and determined the glucose and nitrogen excretion. From the urine nitrogen excretion it is possible to calculate what the glucose excretion should be if 45% of the protein is converted into this carbohydrate. This proportion is taken since the glucose-nitrogen ratio of the totally depancreatized cat is 2.8 to 1. The difference between the calculated amount of glucose and that actually found should represent the glucose derived from protein that is retained in the body. Although we found that this is often a considerable part of the

*It has been observed that when these animals are exhibiting hypoglycemia "normal" glucose tolerance curves may be obtained. More extensive investigations of the respiratory metabolism under these conditions are indicated.

glucose derived from the metabolized protein, yet in reality it only amounts to about 1 to 2 gm. per kilo a day.

The most important test is the change in the respiratory quotient when glucose is given. So far we have not carried this out in our cats, but Houssay[11] has made some determinations upon his dogs. Although he concludes that there is a significant increase in the respiratory quotient, many of us would hesitate to draw conclusions from the small changes he reports in the majority of animals. Furthermore, with one exception, typical diabetic blood sugar curves were found to follow the ingestion of glucose.

I think it is best that for the present we assume that hypophysectomy does not produce any major alteration in the utilization of carbohydrate. In other words, the defect produced in carbohydrate utilization by the deprivation of insulin is not restored by withdrawal of the hypophyseal hormones.

What then is the nature of the alteration produced in the diabetic metabolism? It is at least twofold. *A*, The absence of severe ketonuria, as we have already noted, implies that either acetone bodies are not produced in their usual large quantities or else their complete utilization is restored. Experiments to decide between these alternatives have not yet been done. *B*, the markedly decreased urinary glucose and nitrogen excretion indicates that the usual increased formation of glucose from protein (gluconeogenesis) that occurs when the pancreas is removed is much reduced.

Are the Other Endocrine Glands Involved in the Diabetogenic Action of the Anterior Pituitary Hormones? We have already pointed out that in a large number of instances the anterior pituitary hormones exert their effect by a trophic control of the secretion of another endocrine gland. Is this so in the case of the diabetogenic activity of the anterior pituitary? Before proceeding it would be as well to define what we mean by diabetogenic activity. I have chosen to speak of it here as the capacity of anterior pituitary extracts to increase the glucose, nitrogen and acetone body excretion of a hypophysectomized-depancreatized animal.

If the diabetogenic activity is a trophic one, over what glands of internal secretion is this effect exerted?

There are at least three possibilities. *A*, The thyroid. Houssay[5, 8] has shown that pancreatic or phloridzin diabetes appears to its full extent in thyroidectomized animals. It has, however, been claimed that thyroidectomized rats do not develop ketonuria when injected with anterior pituitary extracts. Further work is indicated upon the possibility that the thyroid may be participating in these phenomena. *B*, The adrenal medulla. The discovery of the glycosuric action of epinephrin by Blum in 1891, followed by the views of Falta, Eppinger and Rudinger that the adrenal medulla participated in the pathogenesis of diabetes mellitus focussed attention upon epinephrin as a diabetogenic hormone. All work to date

refutes this view. It is furthermore unlikely that the anterior pituitary produces its effects by stimulation of this organ since the adrenal medulla is not involved in the general glandular atrophy following hypophysectomy. Other reasons for excluding this organ will be given below.

The only remaining endocrine gland to which some participation in metabolism has been assigned is, *C*, the adrenal cortex. The work of Lukens and myself indicates that if the diabetogenic effect of the anterior pituitary is a trophic one, then this trophic effect is probably mediated by the adrenal cortex.*

The Effects of Adrenalectomy Upon Pancreatic Diabetes. We have successfully prepared a number of totally adrenalectomized-depancreatized cats that have survived for 2 to 4 weeks.[12] These animals exhibit an amelioration of the diabetes comparable to that observed in the hypophysectomized-depancreatized group. We have also prepared a series of animals from which only the adrenal medullæ were removed, and at a later date the pancreas. Such animals do not show any amelioration of the diabetic state, thus conclusively demonstrating that it is the removal of the cortex of the gland that is responsible for the effects of adrenalectomy upon experimental diabetes in the cat.

While it is possible that both hypophysectomy and adrenalectomy ameliorate a diabetes by alterations of the metabolism at different points, this is thought to be unlikely. The fact that adrenalectomy and hypophysectomy are of equal efficiency in this respect together with the marked atrophy of the adrenal cortex following hypophysectomy strongly suggest that excision of either of these endocrines is producing its effect on diabetes by alteration of the same phases of metabolism. As a consequence it may be argued that hypophysectomy produces its effects upon experimental diabetes by reason of the accompanying hypofunction of the adrenal cortex. By analogy with the relationship between the hypophysis and the thyroid extracts of the anterior pituitary capable of increasing the severity of the diabetes in hypophysectomized-depancreatized cats should have but little effect in the adrenalectomized-depancreatized animals.

To test this hypothesis we have taken 9 animals of each type and injected them with a potent anterior pituitary extract. Of the 9 hypophysectomized-depancreatized cats, 4 relapsed into diabetic acidosis and coma and died following the injection. Four others exhibited a markedly increased ketonuria, but recovered.

* In connection with this question Houssay and his co-workers[13] have stated that removal of the adrenals, thyroid, gonads or the gastro-intestinal tract does not prevent the hyperglycemic action of anterior pituitary extracts in the toad. These workers found in this animal that the presence of the liver was necessary. In the dog denervation of the adrenals or thyroidectomy likewise did not prevent the glycosuric action of this extract. No experiments are reported upon completely adrenalectomized animals.

One animal tested a few days before death from inanition did not respond.

By contrast, of the 9 adrenalectomized-depancreatized cats receiving the extract, 8 did not show any alteration in the diabetic condition, the other had an increased ketonuria but was proved to possess an accessory cortical body at autopsy.

The effect of the anterior pituitary extract upon glycosuria was not as striking in our hypophysectomized-depancreatized cats as was its effect upon ketonuria. Nevertheless a definite increase in glucose excretion occurred in about one-half the animals, while no comparable alterations were observed in the adrenalectomized group.

Although this result would appear to establish the trophic nature of at least the ketogenic principle of anterior pituitary extracts, yet there is one factor present in the adrenalectomized-depancreatized cats that calls for further consideration. This is: to what extent is this group of animals suffering from a deficiency of the hormone of the adrenal cortex that we know exercises a marked influence over the sodium and water balance of the body?

We have attempted to control this factor in two ways. *A*, All the animals in which the adrenal and pancreatic tissue was excised at the same time have received daily injections of extracts containing the above cortical hormone. It is true that some of our first preparations received what we now know to be inadequate amounts, but nevertheless they all received some, and we have not observed any striking difference except in period of survival between the diabetes of the inadequately and adequately treated animals. *B*, In another series of 4 animals, the adrenals were first removed and the cats were maintained in good health for periods of from 7 to 28 days before pancreatectomy. The ensuing diabetes of this group in no way differed from that of the former, and neither was the severity of the diabetes increased by doubling the daily injection of cortical extract or by the injection of anterior pituitary extract.

These experiments cast doubt upon the possibility that the amelioration of an experimental diabetes is due to a deficiency of the cortical hormone concerned with water and salt metabolism. Taken in conjunction with the experiments of Harrop *et al.* which demonstrated the development of a severe hypoglycemia during fasting in adrenalectomized dogs maintained with cortical extract, they strongly suggest that the defect in carbohydrate metabolism produced by adrenalectomy is due to the absence of some other substance normally present in the adrenal cortex. As further evidence for this point of view it may be pointed out that injection of the salt and water controlling hormone of the adrenal cortex into hypophysectomized animals does not alleviate their disturbed carbohydrate metabolism. Finally, hypophysectomized animals do not exhibit cortical insufficiency due to sodium loss, yet nevertheless show a striking alteration in their response to pancreatectomy.

If this view is correct, then the adrenal cortex may contain at least two hormones: *a*, one, already described, that appears to control specifically the sodium (and water) metabolism and, *b*, this at present hypothetical entity whose function is particularly concerned with the production of glucose from protein and possibly of certain aspects of the metabolism of fatty acids. It should be clearly understood that the existence of a second principle in the adrenal cortex is so far only a matter of inference, since no one has as yet demonstrated the ability of adrenal cortical extracts to reëstablish the fully diabetic condition in adrenalectomized-depancreatized animals. Until such time as this is accomplished it is important to remember that the possibility still exists that adrenalectomy may produce its effect upon pancreatic diabetes by altering the normal secretory activity of the anterior pituitary.

Other Effects of Adrenalectomy Upon Carbohydrate Metabolism. The evidence for the participation of the adrenal cortex in carbohydrate metabolism is not entirely based upon the effects of the removal of the adrenal glands upon experimental diabetes.

As I have mentioned before, hypophysectomized and adrenalectomized animals develop severe hypoglycemia when fasted. In this condition the blood sugar level has to be maintained by the conversion of protein into glucose. It is also significant that such animals have a decreased nitrogen excretion under these conditions.

Since the work of von Mering, it has been known that the injection of the glucosid phloridzin into animals either fasted or on a protein diet caused marked glycosuria, elevated nitrogen excretion and ketonuria. The urinary glucose-nitrogen ratio becomes constant, which has been interpreted to indicate that all the glucose derived from protein has been excreted. The mechanism by which phloridzin produces this condition is probably by altering the permeability of the renal tubules to glucose so that the organism is unable to retain this substance. As a consequence, both protein and fat metabolism are stimulated.

The difference of opinion as to the manner in which these increases are brought about have been the subject of the same controversy as has existed in the explanation of the effects of total pancreatectomy.

Since phloridzin and pancreatic diabetes present to a large extent the same perversions of metabolism, it is not surprising to find that both hypophysectomy and adrenalectomy markedly alter the response of animals to the injection of this glucosid. Thus Houssay and Rietti[5] have shown this to be so in hypophysectomized dogs and Dr. Gerald Evans,[14] in my department, has shown it for adrenalectomized rats. In both instances it has been observed that the degree of glycosuria, nitrogen excretion and ketonuria is much smaller than is found in normal animals.

There is one other condition in which the formation of carbohy-

drate from non-carbohydrate sources has been demonstrated. This was also discovered by Dr. Evans.[15] If rats are fasted for 48 hours their liver glycogen is reduced to a low level (0.3%). On the other hand, if after a preliminary fast of 24 hours in air, they are then placed for a further 24 hours in an atmosphere of 10.5% oxygen the liver glycogen is greatly increased (up to 1.5 gm. %). This increase in liver glycogen is not derived from the muscle glycogen, since this is also slightly increased, and is accompanied by an increased excretion of nitrogen, indicating that this newly formed carbohydrate had its source from protein. Rats from which all adrenal medullary tissue has been removed show the same changes but not if they have been hypophysectomized or adrenalectomized.

We have seen then that four procedures by which glucose formation from protein is stimulated, to wit, pancreatectomy, fasting, phloridzination and exposure to low oxygen tensions, are relatively ineffective in the absence of either the hypophysis or the adrenal cortex.

Glandular Relationships. Cushing has said, "Endocrinology lends itself to two glaring faults, one the popularization of writing on the subject, and the other a tendency of clinical observers to draw upon their fancy in a symptomatology which does not lend itself to precision."

Knowledge of glandular interrelationships is best gained by first acquiring exact information of the physiologic and biochemical changes produced in the organism by hypofunction or hyperfunction of the individual endocrine organs. Secondly, these effects should be placed on a quantitative basis wherever this is possible. In the case of several of the internal secretions this knowledge is at present not available. Finally, the treatment of glandular disorders only becomes possible when the various hormones have been obtained in a relatively pure form and their dosage accurately determined and standardized.

The multiplicity of hypothetical pluriglandular syndromes that have been described, together with the irrational and unphysiologic methods of treatment by pluriglandular prescriptions, has for many years served to discredit a branch of medicine of which none holds greater promise for future advancement.

The time has now arrived when, chiefly by the efforts of physiologists and biochemists, clinical endocrinologists are beginning to cope with the problems of glandular dysfunction in a rational manner.

The excision of an endocrine gland or the injection of large amounts of its hormone gives us a fairly adequate picture of the condition produced by a hypo- or hyperfunction of this particular organ. The effects of hormonal deficiency or excess are complicated by the possibility that these effects are not confined to one particular

endocrine organ, but induce corresponding and simultaneous alterations in the activity of the other endocrines.

From what I have said this is particularly so in the case of the anterior pituitary. The extirpation of this organ or the continued injection of its extracts is followed not only by marked anatomic changes in the other endocrines, but equally great functional alterations. "All pituitary syndromes are essentially polyglandular" (Cushing).

In the case of the anterior pituitary the concept of functional interglandular relationship is fully exemplified, but it should be reiterated that the control of the anterior pituitary is essentially a trophic one and its hormones (with perhaps one or two exceptions) do not directly bring about any physiologic alteration in the organism.

Conversely, gonadectomy, thyroidectomy or adrenalectomy are followed by structural changes in the anterior pituitary. If these anatomic changes are shown to be accompanied by corresponding deviations in physiologic activity then we are confronted by the possibility that alterations in the degree of activity of any endocrine may, through affecting the anterior pituitary, bring about a generalized polyglandular derangement.

We have now to ask ourselves whether these endocrines whose secretions directly alter the bodily functions ever exhibit interrelationships comparable in any way to those manifested by the pituitary. As you are aware, a large number of such relationships between pairs of endocrine glands have been postulated on clinical grounds and in some cases with good experimental background.

In analyzing these types of relationships two possibilities present themselves. *A*, The hypo- or hyperfunction of a particular hormone may so alter the metabolic background of the organism that the secretions of other endocrines produce an abnormal effect. This is particularly well exemplified by the response of the blood sugar to insulin or epinephrin in hyperthyroid states. This response may not only be greatly magnified, but may even be reversed, depending upon the degree of carbohydrate depletion that has resulted from the hyperthyroidism. Under these conditions we cannot assume that hyperthyroidism has induced alterations in pancreatic or adrenal medullary function, indeed, there is no evidence that this ever occurs. *B*, The dysfunction of one endocrine organ brings about changes in the secretory activity of one or more other endocrines. We have already discussed the anterior pituitary relationships of this type but have still to consider interrelationships of this kind among the other internal secretory glands.

It is probably fairest to state that such relationships do exist, but that the evidence advanced for them is in many instances extremely meager. Consequently, it is not profitable at the present time to attempt to analyze the large number of these supposed

interrelationships. The question of their authenticity will have to await the work of future years.

I have repeatedly emphasized the dominant rôle of the anterior pituitary. So extensive is its influence over the endocrine system that no type of glandular interrelationship of the above type can be established without a most scrupulous examination of the possibility that this supposed interrelationship is not in reality linked through the anterior pituitary.

There is still one aspect of hormonal action that should be touched upon. This is the recent concept of Collip[16] of the existence of "anti-hormones." These substances have up to the present been demonstrated in the case of the growth, gonad, thyroid and ketogenic principles of the anterior pituitary. No anti-hormone has so far been demonstrated for an "effector" hormone such as insulin, estrin or parathyroid, and Collip is of the present opinion that anti-hormones are confined to the trophic hormones.

Collip has also introduced the idea that the effectiveness of a trophic hormone is determined by the ratio between its concentration and that of its corresponding anti-hormone. Thus, if the normal effective stimulus to the thyroid is a 2 to 1 ratio between the thyrotropic and antithyrotropic hormones a hyperactive thyroid might be produced by an increase in the amount of thyrotropic substance or by a decrease in the amount of antithyrotropic hormone. If this principle is a correct one, it greatly adds to the possibility of the occurrrence of smaller changes in endocrine function in contrast to the gross changes that must follow complete removal of an organ of internal secretion.

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STUDIES IN DIABETES MELLITUS.

IV. ETIOLOGY. PART 1.*

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THE first three papers[1] presented the main outlines of the changing picture in diabetes throughout the world. Attention is now directed to the diabetic patient, in particular to the group treated by Joslin and his associates at Boston. This diabetic group is unique and valuable because (1) going back as it does to the year 1897, it covers the several periods in which important advances have been made in the knowledge and treatment of diabetes; (2) it is an experience under the observation of a single individual over a period of 35 years; (3) periodic contact has been maintained with practically all these patients; and (4) the size of the group permits numerical analyses which for many items are statistically significant.

After a general description of the group, the major part of the paper relates to the facts on etiology of the disease in this group of patients with emphasis largely on those elements which lend themselves to statistical representation.

General Features of the Group Studied. We believe that this group is a fairly representative cross-section of the diabetic population. It has been recruited chiefly from the middle classes, with others about equally divided between private-room and free patients, although each individual in it was treated as a private patient.

* Part 2 will appear in the July issue of this journal.

Both sexes and all ages were represented, but the number of children is relatively large, because of the senior author's interest in diabetic children. The proportion of males, too, is relatively high, but not to a degree sufficient to bias the experience or the results based thereon. In this regard, it is, in fact, more representative than most reported clinical experiences.

Intensive study has been made of 6357 patients who were discharged from Dr. Joslin's service during the years 1897 to 1928, and in addition 463 diabetic children treated in the period 1929 to 1934, inclusive. For much of this time Drs. Root, White and Marble have been concerned in their study and care. The records of adult patients seen since 1928 also have been used in some instances. The number quoted includes only those patients who were diagnosed as diabetic according to the best current standards. At the beginning, the diagnosis was based upon a definite glycosuria and the typical symptoms of diabetes, loss of weight and strength, polydipsia, polyuria, polyphagia and pruritus. About 1915, when the series had reached 1000 cases, the level of the blood sugar was added to the diagnostic measures and many earlier cases eliminated. As knowledge of its normal and abnormal variations became known, the blood sugar became of increasing importance in the diagnosis and, in 1927, the entire series was reclassified.

The criteria for the diagnosis of diabetes in recent years have been a venous blood sugar of 0.14 mg.% or more fasting and 0.17 mg.% or more after a meal, with a simultaneous glycosuria definitely related to diet. A large number of referred cases who were not diabetic according to the criteria used are excluded from this study. They will be the subject of a later paper.

The group studied includes all the diabetic patients seen during these years, namely, in the hospital (chiefly the New England Deaconess Hospital and recently at its George F. Baker Clinic), at the office and in consultation. The two latter groups, many of whom were seen only once or twice, are fairly large. Despite this, periodic contact has been kept up with all of them either through their physicians or by direct communication. Thus, of the 6357 patients discharged up to the end of 1928, the condition of 6321 (99.4%) was known as of the anniversary date of discharge in 1929. Again, of the 2397 diabetics treated prior to the beginning of insulin treatment in 1922 and traced as of January 1, 1934, information was obtained on 2373 (99%). Thus, even of this group who were seen originally from 12 to 35 years ago, only 24 (1%) were untraced.

Record Card. The record card used in the analysis of this experience is reproduced on p. 761. On it were abstracted from the senior author's records the data pertinent to this study: (1) Essential items of description; (2) family history of diabetes; (3) facts relating to the onset; (4) significant items in the personal history; (5) clinical

FACE:

CHART I.

POST-TREATMENT HISTORY OF DIABETICS

E. P. JOSLIN, M.D., Boston, Mass.

CASE NO.....

1. AGE AT EXAM.:	2. DATE OF EXAM.:	3. DATE OF BIRTH:	4. RESIDENCE OF PATIENT (CITY AND STATE):	5. CAUSE OF EXAM. INS. ROUT.

6. SEX:	7. MAR. COND.:	8. NATIONALITY OR RACE:	9. OCCUPATION:	10. DIAGNOSIS: D.M. R.G. P.D. UNC.

11. FAMILY HISTORY OF DIABETES.

F. M. CH. S. B. SP. OTHER (SPECIFY)

12. PAST HISTORY (FOR PATIENTS UNDER 10 AT ONSET):

AGE AT ATTACK→ S.F. R.F. TONS. DIPH. MSLS. MPS. PERT.

13. ONSET: A. DATE	B. AGE	C. HEIGHT C	D. WEIGHT D	E. PREVIOUS MAX. WT. D	F. SUGAR DISCOVERED
		FT....IN. S	LBS. N	LBS. N DATE.....	DATE.....

14. ETIOLOGY:

A. OB.	B. HER.	C. GLANDULAR	D. BILIARY TRACT	E. MISC.

15. EXAMINATION:

TEETH

GEN. APP.: HT.....FT.....IN. C S WT.....LBS. D N THYR.

PULSE: ART. 0 1 2 3 4 BL. PR. TONS. EYES

HEART: ABD.

LUNGS: DORS. PED. R. L.

16. BLOOD WASS.....SUGAR: FASTING....P.C.....HRS..... 17. URINE: ALB.....DIACETIC.....SUGAR.....

18. DISTINCTIVE FEATURES AND COMPLICATIONS:

19. TREATMENT

HOSP.	IF HOSPITALIZED	OPERATIONS	DISCHARGE DATA	INSULIN.....UNITS	P
CONSULT.	DATE ADM.....		DIET: C.....P.....F.....CAL.		P.P.
OFFICE	DATE DIS.....		BL SUGAR: FASTING...P.C....HRS.....		N

REVERSE:

POST-TREATMENT RECORD

	DATE	HEIGHT (IF UNDER 20)	WEIGHT (IN LBS.)	OCCUPATION	INSULIN (UNITS)	URINE: SUGAR	CONDITION
1		FT. IN. C S	D N				
2		FT. IN. C S	D N				
3		FT. IN. C S	D N				
4		FT. IN. C S	D N				
5		FT. IN. C S	D N				
6		FT. IN. C S	D N				
7		FT. IN. C S	D N				
8		FT. IN. C S	D N				
9		FT. IN. C S	D N				
10		FT. IN. C S	D N				

MORTALITY DATA: DATE OF DEATH

CAUSE: PRIMARY.....

SECONDARY.....

.....

TERMINAL CONDITIONS

IF COMA: INSULIN..... UNITS

CAUSE.....

findings on examination; (6) summary of treatment on first admission; (7) follow-up history after discharge.

It will be noted that the name of the patient is not abstracted on the record card. The follow-up section of the card permits entries for periodic observations.

Residence. The very great majority of these patients resided in the northeastern section of this country: 85% lived in New England, 67% in Massachusetts, 41% in the Boston Metropolitan District and 14% in Boston itself. Of the 15% who lived outside New England, nearly half came from the three nearby states, New York, New Jersey and Pennsylvania. A negligible proportion came from other parts of the country, and of the few foreign patients, most of them were from the Canadian provinces bordering on New England. This is particularly true in the case of women. The concentration of so large a number of patients within a relatively small geographic area is, in some measure, an indication that this practice gives a good cross-section of the several social and economic classes, but we shall see this more fully later.

Nationality of Patients. The patients were predominantly of native birth; practically all of the children were American born. Of the adults for whom these facts were recorded, 65.9% of the men and 59.1% of the women were native born. This figure excludes, however, a small percentage of Jewish patients of native birth. Jewish patients who have been classified together regardless of their country of origin, form the second largest group, namely, 14.2% of the men and 18.9% of the women. The proportion of Jewish cases was far in excess of their proportion in the population of this area (about 8%).[2] The only other nationalities represented by considerable numbers were Canadians, Irish and English.

The percentage recorded as native born was lower in the later years of this experience than in the earlier years. The increase in the other nationalities was not concentrated in any single racial or national group. The only one to show an important change was the Italian. The percentage of Jewish cases among male patients increased somewhat, but this did not hold for females. The decline in the percentage of native born and the corresponding increase in other nationalities was due, in large measure, to changes in the population from which our material was drawn, and reflects the great wave of immigration in the three decades prior to 1914. The new immigrants have only recently attained, in large numbers, the ages at which diabetes is prevalent.

Occupation. Another feature which stamps the experience as fairly representative is the occupations of the men. As might be expected, these patients include a rather large proportion of proprietors, officials and managers, and members of the professions, particularly physicians. But there is a goodly representation of the common occupations, as, for example, the building trades and

other skilled workers, viz., tailors and printers, clerks, policemen, factory workers, store clerks and salesmen.

TABLE 1.—NATIONALITY OR RACE OF A GROUP OF ADULT DIABETICS. PER CENT OF EACH NATIONALITY OR RACE TO TOTAL OF KNOWN ORIGIN. BY SEX AND CALENDAR YEAR PERIODS. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Nationality or race.	Males.					Females.				
	1897–1928.	1897–1914.	1915–1919.	1920–1924.	1925–1928.	1897–1928.	1897–1914.	1915–1919.	1920–1924.	1925–1928.
American (white)	65.9	77.0	70.9	66.5	61.3	59.1	69.8	61.5	60.4	56.7
Canadian	5.7	1.1	6.6	3.3	8.2	5.2	1.5	5.3	4.4	6.3
Jewish	14.2	12.2	11.6	14.7	15.2	18.9	18.8	19.2	20.3	17.7
English	2.6	2.2	2.4	2.7	2.7	2.2	...	1.1	1.3	3.3
Irish	3.0	3.9	1.9	3.3	3.1	5.1	6.0	3.2	5.1	5.4
German and Austrian	0.5	...	0.5	0.5	0.5	1.1	0.8	1.1	0.8	1.3
Scandinavian	1.1	0.5	0.5	1.2	1.3	0.8	...	0.4	0.8	1.0
Scotch	1.0	...	0.8	1.7	0.7	1.1	0.8	0.7	0.9	1.4
Italian	1.7	0.5	1.1	1.3	2.6	2.1	...	1.8	1.8	2.7
Russian, Polish and Lithuanian	0.6	...	...	0.2	1.3	0.6	...	...	0.5	0.9
Colored	0.2	0.5	...	...	0.5	0.4	0.8	...	0.3	0.5
Others	3.5	2.1	3.7	4.6	2.6	3.4	1.5	5.7	3.4	2.8
Number of cases:										
Total	2,779	382	400	906	1,091	2,914	263	304	1,032	1,315
Known nationality	2,411	182	378	837	1,014	2,617	133	281	965	1,238

Of 2304 patients whose occupation was definitely known, 18.6% were foremen, mechanics, operatives or laborers in manufacturing industries. Owners and managers in these industries constituted 6.5% of the total. Retail merchants were numerous, 12% of the total; but this is not surprising in view of the large number of Jewish patients. The other large groups of the proprietor class consisted of those in finance and wholesale trades, 7.2%, and farmers, 4.8%. Other sizeable groups in the working class included chauffeurs and teamsters (1.5%), employees of steam and street railroads (1.7%), store clerks and delivery men (5.6%), clerks (4.3%), government employees (2.8%) and domestic and personal service workers (2.4%). The proportion engaged in professional and semi-professional pursuits was large. On the basis of the total with known occupations, the proportion was 21.8%. Naturally, in an experience of this type the number of physicians and surgeons was large, 6.9%. They constitute an important group, (1) because on the whole they follow treatment more carefully, and (2) because end results of treatment can be obtained very readily. The authors believe that next to children this group is the one most worthy of investigation. Important aspects regarding diabetic physicians in this series will be presented in the course of later papers.

Reason for Initial Examination for Diabetes. Most of these patients were first examined for diabetes because of the development of symptoms of the disease. A large number, however, were diagnosed, while still symptomless, as a result of examination for life insurance. Of the adult patients first seen between 1897 and

1928, 426 were discovered in this manner. Among men, these insurance cases account for 12.6% of the total and among women, 1%. If we consider only what may be termed the insurable ages, 20 to 64 years, the percentages are 15.9 and 1.3, respectively. Among men, at ages 35 to 44, no less than 21.3% were so discovered. The actual number of patients discovered as a result of an insurance examination has steadily increased, although the proportion of such cases to the total was highest between 1920 and 1924. Of those cases referred for diagnosis, but found to be not diabetic, insurance cases form an even larger proportion, namely, 25.3% of the men and 3.1% of the women. Approximately two-thirds of those referred for diagnosis because of glycosuria on insurance examination were found to be diabetic.

TABLE 2.—DISCOVERY OF DIABETES BY INSURANCE EXAMINATION. PER CENT OF CASES. BY AGE, SEX AND CALENDAR YEAR PERIODS. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Age at examination.	Males.					Females.
	1897–1928.	1897–1914.	1915–1919.	1920–1924.	1925–1928.	1897–1928.
All ages	12.6	7.0	12.0	14.7	13.0	1.0
20–64	15.9	8 3	14 8	18.7	16 8	1.3
Under 20	0 6	.	...	0 8	0.8	...
20–34	12.7	12 5	9.7	13 8	13 1	2.8
35–44	21 3	6.3	20.0	28.9	21 4	2.4
45–54	19 1	9 1	17 7	22 6	20 8	0.8
55–64	11 9	6.5	10.5	12 9	13 3	0 8
65 and over	4 3	4 4	5 5	4 0	4.2	0 4
Number of cases	3,124	428	449	1,034	1,213	3,233

These insurance cases are important for two reasons: (1) they tend to be recently developed cases and, consequently, relatively free from complications; (2) the percentage of these cases is highest in adult and middle life, where the disease, if untreated, tends to be somewhat severer than cases in later life. Early diagnosis is, consequently, of vital importance in these cases. Thus, of the adult male insurance cases, 70.6% were between ages 20 and 54 when diagnosed, but only 49.4% of all cases were in this age group. We shall show later the value of early diagnosis of these cases when we compare the mortality among them with that in other cases. The large proportion of these cases discovered early by insurance undoubtedly influenced the results of treatment in this practice.

The Etiology of Diabetes. *Viewpoint and Method of Analysis.* The factors which have been suggested as entering into the etiology of diabetes are many: heredity, obesity, arteriosclerosis, gall-bladder disease, nervous strain, pituitary disease, thyroid disease and other

conditions. It has been suggested even that there are several types of diabetes; that the diabetes of childhood, of middle life and old age are distinct entities. It is the belief of the authors, however, that there is an essential unity in diabetes and that this unifying factor is heredity. The other factors are essentially of the nature of excitants of the disease. Heredity determines the susceptible individuals, but since the disease is rarely, if ever, present at birth, it is reasonable to postulate at least one or more other factors which act to bring out the inherited predisposition. On this basis, the essential difference between the diabetes of the several ages of life may reflect only the typical age incidence of the various excitants.

Some of the factors, moreover, seem more and more to be linked. The nature of this relationship reflects the newer concept of diabetes as involving not only the islands of Langerhans, but other organs, if not the whole endocrine system of the body. Without destroying the validity of this view of heredity as the unifying factor, however, it is possible that isolated cases may have no hereditary background, such, for example, as might be the diabetes resulting from hemochromatosis, although the heredity is unusually strong in this group. Perhaps it is only the hereditarily predisposed hemochromatosis patient who develops diabetes.

This theory of the unity of diabetes is in our opinion correct, but in the present state of our knowledge, not fully demonstrable. Certainly all of the elements which contribute to the proof cannot come out of a purely clinical experience. Much of it depends upon work in several scientific fields, especially in experimental biology, pathology and biochemistry. While much has been or is being done, the fundamental researches are far from complete. Within the limitations described, the present paper seeks to show what light can be thrown on the problem by this clinical experience, supplemented by the results of investigations in the other related fields. Our approach to the problem is through an analysis of the constitutional factors and medical history of the diabetic patient at the onset of the disease. The discussion of heredity is deferred to the next paper because it cannot be treated adequately as part of the present one.

Physical Characteristics at Onset. *Sex.* The first important and striking feature in the makeup of diabetic patients is the peculiar sex incidence of the disease. Of the 9853 patients seen between 1897 and 1933, 4639 were males and 5214 females. The females thus outnumbered the males by 12.4%. There has been a considerable change in this respect as time has progressed. In the early years of this experience there was a marked excess of males, and even up to 1922 the number of male patients was somewhat greater than that of females. Since that date the number of female patients has been larger and the disparity is definitely increasing. Thus, for the years 1925 to 1928 there were 20% more females than

males, but in 1929 to 1933, 30.8%. As compared with the sex incidence in diabetes mortality, the proportion of females in this experience, even in recent years, is low. For, the death rate from diabetes, as we have seen, is 50% or more higher for females than for males, both in the country as a whole, and in Massachusetts. Such differences in the proportions of males and females, however, are common in clinical experiences (Table 3). The preponderance of male diabetics in older and even in some recent clinical experiences is probably due to the greater frequency with which men seek expert medical care. In this particular series it is to some extent due also to the interest of the senior author in younger patients where there is little difference between the sexes in the incidence of diabetes.

TABLE 3.—SEX INCIDENCE OF DIABETES IN RECENT CLINICAL EXPERIENCES.

	Number of patients.		Females per 100 males.
	Males.	Females.	
Joslin (Boston)—1897–1933	1,639	5,214	112.4
1929–1933	1,515	1,981	130.8
1925–1928	1,213	1,456	120.0
1920–1924	1,034	1,128	109.1
1915–1919	449	350	78.0
1897–1914	428	299	69.9
Barach[4] (Pittsburgh)—1925–1935	264	321	121.6
Cammidge[5] (London)—1934*	598	402	67.2
Gotten[6] (Memphis)—1920–1930	88	61	69.3
John[7] (Cleveland)—1921–1927	928	1,058	114.0
1925–1927	469	531	113.2
1921–1925	459	527	114.8
Mayo Clinic:			
Wilder[8]—1931–1934	1,248	958	76.8
Allan[9]—1930	478	362	75.7
Adams[10]—1926*	571	429	75.1
Palmer[11] (Seattle)—1919–1934	333	380	114.1
Sevringhaus[12] (Milwaukee)—1922–1930	252	248	98.4
Wendt and Peck[13] (Detroit)—1919–1929	379	694	183.1
Wright[14] (Clifton Springs, N. Y.)—1926	123	133	108.1

* Publication date.

Age at Onset. Mortality data presented in an earlier paper[3] indicate a characteristic age distribution in diabetes; the death rate, regardless of sex, increases steadily throughout life, reaching a maximum in old age. Since diabetes is a chronic disease, however, the age at onset is much more important than the age at death. Consequently clinical records give a much truer picture of this characteristic of the disease than do mortality records. The time of onset of diabetes, as is well known, is not usually definite, especially in the milder cases occurring in later life, but it can be fixed with reasonable accuracy in most cases.

In searching for the date of onset in this series the date of diagnosis

furnished the starting point in the majority of instances. In many it was necessary to use this date as that of onset, but often the type of onset as described by the patient would be helpful, namely, whether *sudden*—in the course of 24 hours; *rapid*—in the course of a week; *gradual*—during a period of 2 months; or just *indefinite*—over a longer period of time. In the latter instance the time of the development of symptoms would be helpful. When doubt existed it was the rule to choose the shortest probable interval between onset and diagnosis.

In this experience the number of patients increases steadily from infancy to a maximum at ages 50 to 54 (Table 4), except for a slight dip in the late teens. The rise is resumed in the late twenties and increases rapidly until middle life. The incidence drops off rather sharply from the peak as old age is approached. Relatively few cases are recorded as having their onset in the eighties and none has been found with onset after age 85.

TABLE 4.—AGE AT ONSET OF DIABETES. PER CENT DISTRIBUTION OF CASES WITH KNOWN AGE AT ONSET. BY SEX. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Age at onset.	Males.	Females.
All ages	100.0	100.0
Under 5	2.1	1.6
5– 9	2.9	2.8
10–14	3.8	3.5
15–19	3.3	2.6
20–24	4.0	2.4
25–29	5.3	4.2
30–34	6.6	4.4
35–39	8.1	6.8
40–44	10.3	9.7
45–49	12.7	14.3
50–54	14.4	15.7
55–59	10.7	13.6
60–64	8.7	9.2
65–69	3.8	5.8
70–74	2.2	2.1
75–79	0.9	1.0
80–84	0.2	0.2
85–89		0.1
Median age (years)	46.4	49.2
Number of cases	3,119	3,229

At the younger ages, the number of cases is approximately equal for both sexes. Indeed, at most ages up to 45 the males outnumber the females. Beginning with 45, however, the order is reversed and the number of females is much larger than that of males up to age 70. In old age the numbers are again approximately the same.

The age distribution at onset (Table 5) has changed perceptibly. There has been a definite increase in recent years in the proportion

of patients at the older ages, past 60 among males and past 50 among females. The median age at onset has increased, between 1897 to 1914 and 1925 to 1928, 2 years among males and 4 years among females. These changes, to some extent, reflect the declining proportion of younger persons and the increasing proportion of older persons in the general population. It will be noted that in the period 1915 to 1919 the proportion of males with onset in the third and fourth decades of life is relatively large. This is probably a by-product of the examination of men in these age groups for the draft in the World War.

The point of maximum onset for age (Table 5) has shown little change. Among males this point has shifted between the fifth and sixth decades, but among the latest cases is definitely in the sixth decade. Among females the maximum onset has been in the sixth decade of every period except 1915 to 1919 and has been increasingly well defined.

TABLE 5.—AGE AT ONSET OF DIABETES. PER CENT DISTRIBUTION OF CASES WITH KNOWN AGES. BY SEX AND CALENDAR YEAR PERIODS. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Sex; age at onset.	1897–1928.	1897–1914.	1915–1919.	1920–1924.	1925–1928.
MALES:					
Under 10	5 0	3 8	6 0	5.0	5.0
10–19	7.1	8 0	5.3	8 7	5.9
20–29	9 3	8 3	12 7	10.5	7.3
30–39	14 7	14 9	17 8	13 5	14.6
40–49	23.1	25 5	25 0	24 0	20.7
50–59	25.1	26 3	23.4	23.4	27 1
60–69	12.5	10.1	7 8	12 7	14.8
70–79	3.0	3.1	2.0	1.9	4.4
80–89	0.2	...	...	0.3	0.2
Median age (years)	46.4	46.4	43.4	45.8	48.4
Number of cases	3,119	424	449	1,033	1,213
FEMALES:					
Under 10	4.4	6.4	5.2	4.3	3.8
10–19	6.1	6.1	10.3	4.3	6.5
20–29	6.5	11.1	7.8	7.0	4.9
30–39	11.2	14.5	12.9	10.9	10.3
40–49	24.1	21.9	25.6	25.3	23.2
50–59	29.2	24 9	24.4	30.8	30.3
60–69	15.1	12.1	10 9	14.3	17.2
70–79	3.2	3.0	2.3	3.0	3.5
80–89	0.2	...	0.6	0.1	0.3
Median age (years)	49.2	46.4	45 9	49.4	50.4
Number of cases	3,229	297	348	1,128	1,456

Certain anomalies in the sex and age distribution, particularly among females, are also brought out by the table. Among males, when the experience is divided up into the several calendar periods, the number of cases increases with age up to the maximum in every

period with but a single exception, which can be dismissed as a chance phenomenon due to the small numbers involved. Among females, however, since 1925, the number of patients with onset in the third decade of life has been definitely lower than in the second decade. The reason for this is unknown, but perhaps may be explained on the basis of a preponderance of diabetic children in this series.

TABLE 6.—AGE AND SEX INCIDENCE OF ONSET OF DIABETES. PER CENT DISTRIBUTION OF CASES WITH KNOWN AGES. RECENT CLINICAL EXPERIENCES.

Sex; age groups.	Joslin (Boston), 1925–1928.	Cammidge[5] (London), –1934.§	John[7] (Cleveland), 1921–1927.	Mayo Clinic. Wilder[8] 1931–1934	Mayo Clinic. Adams[16] 1926§	Palmer[11] (Seattle), 1919–1934.	Wendt and Peck[13] (Detroit), 1919–1929.	Barach[4] (Pittsburgh), 1925–1935.*	Rabinowitch[15] (Montreal), 1921–1927.† Total persons.	Sovringhaus[12] (Milwaukee), 1922–1930.† Total persons.
MALES:										
0– 9	5.0	4.7	1.8	3.7	3.2	7.5	3.2	2.3	2.3	3.6
10–19	5.9	6.4	3.1	5.5	6.7	6.9	6.6	5.3	5.5	12.4
20–29	7.3	11.9	5.3	5.8	11.1	6.6	8.4	9.8	6.8	8.0
30–39	14.6	15.9	13.0	12.5	14.2	9.9	18.5	23.1	17.9	10.2
40–49	20.7	27.7	21.8	23.2	17.5	24.4	19.8	24.2	27.5	14.8
50–59	27.1	21.9	26.7	27.8	25.9	23.7	19.3	20.1	25.2	22.0
60–69	14.8	11.5‡	28.3‡	17.4	18.4	14.4	20.2	13.3	11.8	21.4
70–79	4.4	...	...	3.8	2.9	6.3	3.7	1.9	2.7	7.6
80 and over	0.2	...	...	0.3	...	0.3	0.3	...	0.3	...
FEMALES:										
0– 9	3.8	4.7	1.4	4.7	5.5	4.5	0.4	1.6		
10–19	6.5	6.7	2.3	4.2	5.4	5.5	3.7	3.7		
20–29	4.9	10.2	6.2	5.2	7.5	7.1	5.3	5.0		
30–39	10.3	17.7	11.4	12.3	9.9	7.1	13.5	15.3		
40–49	23.2	19.2	24.7	25.4	22.1	23.2	24.9	35.7		
50–59	30.3	24.6	28.9	32.0	29.3	31.3	31.2	25.9		
60–69	17.2	16.9‡	25.1‡	13.8	18.2	17.6	18.3	11.2		
70–79	3.5	...	...	2.4	1.8	3.7	2.7	1.6		
80 and over	0.3	...	...	...	0.2	...	...	...		
NUMBER OF CASES:										
Males	1,213	598	928	1,248	571	333	379	264	1,316	500
Females	1,456	402	1,058	958	429	380	694	321		

* Age at diagnosis.
† Age at admission to hospital.
‡ 60 and over.
§ Publication date.

Comparison of Age at Onset With Other Experiences. The age and sex phenomena in this experience, with the exceptions noted, are believed to be fairly typical. Comparison with other experiences (Table 6) tends, in general, to confirm this observation. It is readily appreciated, however, that such comparisons must be made cautiously because of the subjective element in the determination of onset. One of the advantages of the present experience is that this element is practically constant throughout the 30 odd years, because the senior author made the diagnosis in all cases and fixed the date of onset in most cases, and even in recent years, as a rule, has checked this date. In some of the other experiences, the age data do not always relate to the date of onset, but sometimes to the date of the original diagnosis or of hospital admission, regardless of previous

treatment. In some cases the facts are not shown separately for each sex—a serious omission as there is a fundamental difference in the onset curves of the two sexes. Good material on the age at onset of diabetes is scarce, and it is hoped that this report will stimulate improvement in this regard.

In general, the several experiences (Table 6) agree in the rapid increase with age in the frequency of onset of diabetes. But the maximum is not always the same, nor is it always well defined. In practically all the experiences, the number of onsets at the very old ages is small. The major differences between the several experiences are probably due either to differences in the method of computing onset or in the type of experience. In the hospital experiences, children tend to be relatively numerous, probably because they form a disproportionately large number of the acute cases, especially coma, which receive hospital treatment.

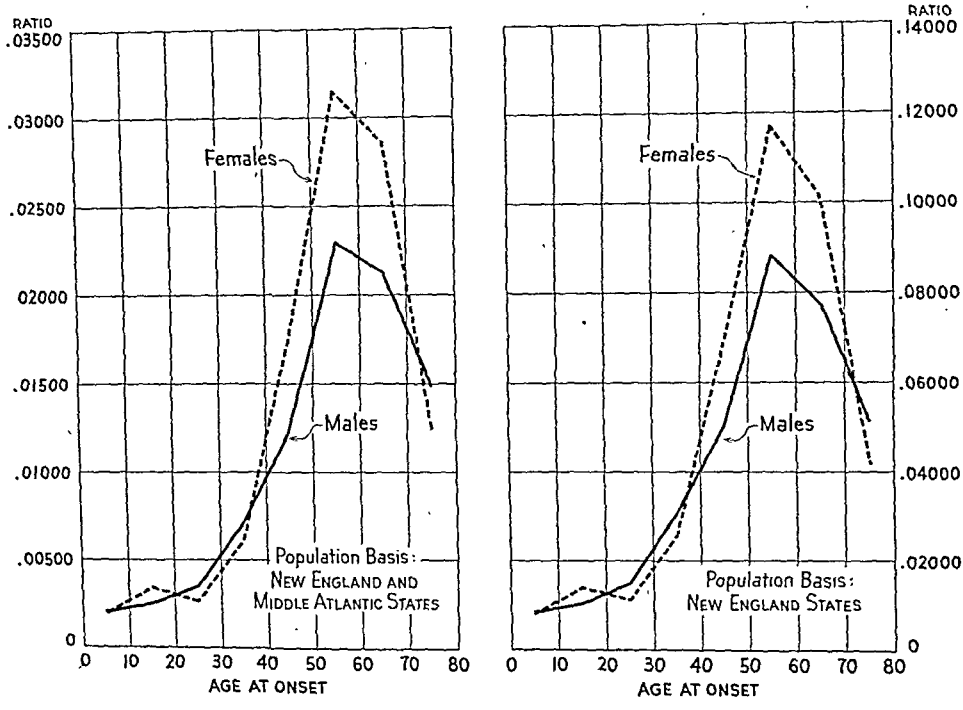
Age Specific Onset Rates. These data on the age distributions at onset in clinical experiences, while adequate as to the numerical frequency according to age, do not represent the rate of onset at each age. For example, the small number of cases at the later ages obviously reflects, to some extent at least, the relatively small proportion of persons at those ages in the general population. The determination of true onset rates according to age is, however, practically impossible, for this would require knowledge of the age at onset by sex for a specific calendar period in a population, the composition of which was known. Obviously, such data are not available and recourse must be made to other modes of analysis.

An original approach to the problem is the estimate by Pincus, Joslin and White[15] of the true proportional age frequencies at onset. Their method consists essentially in weighting the observed frequency of onset in Joslin's experience according to the reciprocals of the proportions surviving to each age of the life table (1_x). While their method gives a better idea of the true profile of the onset curve than the crude figures, it does not permit proper comparison between the relative onset rates of the two sexes, and the life table basis gives undue weight to the older ages.

A more accurate picture is obtained simply by comparing the actual age distribution of the patients in this experience with that of the population from which they are drawn. This has been done by computing ratios of patients to population by age groups. The patients included are those discharged between 1925 and 1928. The analysis was limited to patients seen in this period partly in order to get a more current picture of the situation, and partly because this group is more truly, though by no means entirely representative of the diabetic population than is the entire experience. Two population bases are used, namely, the estimated white population in 1925 of the New England and Middle Atlantic States combined, from which over 90% of the patients came, and the

corresponding population for the New England States only, from which 85% of the patients came. The year 1925 was chosen as an approximate mean year of onset of diabetes in this patient group. This is, strictly speaking, not accurate, but sufficiently close to give trustworthy results. Similar ratios have been computed on the basis of the per cent distribution of the two populations. The derived figures are not true onset rates, but the age relationships are fairly accurate. At the younger ages, they are probably too high, and, after 40, the female curve is certainly too low.

CHART II.—AGE RELATIONSHIPS IN THE ONSET OF DIABETES. RATIO OF PATIENTS OF E. P. JOSLIN, 1925–1928, TO POPULATION OF (*a*) NEW ENGLAND AND MIDDLE ATLANTIC STATES COMBINED AND (*b*) NEW ENGLAND STATES ONLY, JULY 1, 1925 (ESTIMATED). BY SEX AND AGE.



Similar age contours are obtained by all methods. Chart II shows the results based on the ratios of the age distributions. In both sexes the onset rates are lowest in the first decade of life, but rise at first gradually, then very rapidly to a maximum in the fifties, drop off slowly in the next decade, and then rapidly to the end of life. The number of cases recorded in the eighties is too small to show accurately the slope of the curve and the figures, therefore, are omitted from the chart. No onset has been observed in the nineties in this experience; such cases are rare, if they exist at all. Among females there is a definite depression in the curve in the twenties.

When the curves for each sex are compared, it is found that up

to the age of 40 the frequency of onset in males is generally somewhat higher than in females, but from 40 to 70 the frequency of onset in females is appreciably in excess of that for males. During this period of life, when the onset of diabetes is most frequent, the females show a rate of onset approximately one-third in excess of that of males. In the eighth decade, the frequency, based on this experience, seems to be somewhat greater among males, but this is questionable in view of the opposite trend in mortality. The number of cases past 80 is too small to permit a reliable comparison. As we have indicated earlier, the onset curve for females from age 40 on is too low, and the differences between the two sexes, therefore, are actually greater than here shown.

TABLE 7.—INCIDENCE OF JEWISH CASES AMONG DIABETICS. NUMBER AND PROPORTION OF CASES IN SPECIFIED AGE GROUPS. BY SEX. EXPERIENCE OF E. P. JOSLIN, 1897–1928.

Age at onset.	Number.		Ratio of Jews to all cases.		Per cent of all ages.	
	Males.	Females.	Males.	Females.	Males.	Females.
All ages	361	528	11 6	16.3	100.0	100.0
Under 5	4	4	6.1	7.8	1.1	0.8
5– 9	2	12	2 2	13.2	0.6	2.3
10–14	6	14	5 1	12.5	1.7	2.7
15–19	8	10	7 8	11.8	2.2	1.9
20–24	15	11	12.0	14.3	4.2	2.1
25–29	18	17	11.0	12.7	5.0	3.2
30–34	32	32	15 6	22.5	8.9	6.1
35–39	48	53	18.9	24.2	13 3	10.0
40–44	59	70	18.3	22.3	16.2	13.3
45–49	54	101	13.6	21.8	14.9	19.0
50–54	56	101	12.4	19 9	15.4	19.0
55–59	32	61	9.5	13 9	8.9	11.6
60–64	19	26	7.0	8.7	5.3	4.9
65–69	6	13	5.1	7 0	1.7	2.5
70–74	2	2	2.9	2.9	0.6	0.4
75–79	...	1	...	3.0	...	0.2
Median age (years)	44 1	47.0				

Age at Onset in Jewish Patients. Among Jewish patients in this experience, the onset picture is somewhat different from that of other patients. The Jewish patients developed diabetes relatively early. As Table 7 shows, the maximum numerical frequency of onset of diabetes in Jewish males was between 40 and 44, compared with 50 and 54 for all male patients. In Jewish female patients, equal numbers of onsets were recorded in age periods 45 to 49 and 50 to 54, whereas among all female patients the onset peak was definitely at ages 50 to 54. The median age at onset of the Jewish patients was slightly over 2 years less than that of all patients.

Certain other features of the Jewish experience in regard to sex and age are significant. The number of Jewish female patients exceeded that of males up to the end of 1928 by 46.3%, whereas among non-Jewish patients the number of males was actually slightly greater than females. Considered by age, the number of Jewish female patients was far in excess of the males except in the twenties and thirties. In the late forties and in the fifties, the female cases outnumbered the males nearly 2 to 1.

The proportion of Jewish to total patients (Table 7) varied widely by sex and by age. For all ages, Jewish males constituted 11.6% of all male patients, but females, 16.3% of all female patients. Among males, the proportion of Jewish patients to total patients is relatively small at the younger ages of onset, but increases fairly steadily by age up to the maximum of 18.9% in the late thirties and declines steadily thereafter. Among females, the proportion of Jewish patients is larger at every age than among males. Even at the younger ages at onset, the proportion of Jewish females is well over 10% and increases to a maximum of 24.2% in the late thirties. It then declines, at first gradually, and then somewhat more rapidly with advancing age.

This wide difference in the proportion of Jewish patients at the several ages is certainly not due to chance.[17] It reflects, in some measure, merely the percentage of Jews who, in middle life, are better able to afford and seek expert treatment. This, however, can at best be a partial explanation. We believe that the facts on the age at onset of diabetes in Jewish patients fits in with the mortality data given in an earlier paper,[17] which showed that at the younger ages there is little difference in the diabetes death rates of Jews and non-Jews and only past 45 are the Jewish rates excessive. As for the sharp decline in the proportion of Jewish patients at the older ages, it is, in part, due to the fact that the Jewish population, largely an immigrant one, is deficient in the proportion of old people, but even with reasonable allowance for this it seems that Jewish patients are prone to diabetes in early middle life.

Marital Condition in Relation to Diabetes. The incidence of diabetes is higher in married women than in single women. This difference is not found in men. Indeed, only among the married is there a large difference between the sexes in regard to the frequency of diabetes. This was shown by Mosenthal and Bolduan,[18] from New York City mortality data, and is confirmed by similar Canadian data[19] in the period from 1928 to 1932 (Table 8). The significance of the large difference between married and single women in the Canadian experience between ages 25 and 44 is uncertain, because the average age of the single, in this broad age group, is much lower than that of the married. Unfortunately, more detailed data needed to clear up this point are not available. The widowed have higher rates than the married within the broad

age groups studied, but this also reflects in large part their higher average age.

TABLE 8.—DIABETES AND MARITAL STATUS.[19]
Death Rates per 100,000 From Diabetes. By Sex and Age. Canada, 1928–1932.

Marital status.	Ages 25 to 44.		Ages 45 to 64.		Ages 65 and over.	
	Males.	Females.	Males.	Females.	Males.	Females.
Single	4 3	2 2	21 9	19 2	78.2	71.7
Married	3 2	3 9	18 1	33 1	79.3	138.0
Widowed	*	*	30 5	42 8	97.3	127.0

* Not significant because of small number of deaths.

Partial confirmation of the findings regarding the higher frequency of diabetes in married women is afforded also by analysis of the facts on the marital condition of the senior author's group of patients. These have been tabulated as of the date of examination and compared with the marital distribution of the population of New England in 1920, that year being taken as an approximate mean. On this basis, there was a sizeable deficiency from ages 45 on in the proportion of single persons in this diabetic group, as compared with the general population, both among men and women, but more especially among women. At ages under 45, this relationship did not exist, for the proportion of single persons was higher among the diabetics at ages 20 to 24, and among women not greatly different at ages 25 to 44. This is not altogether surprising. To some extent, this is explained partly by the hesitation of young diabetics to marry, but to a far greater extent by the relatively large number of persons in this diabetic group from families in comfortable circumstances, where marriage tends to be delayed.

Mosenthal and Bolduan[18] suggest that the effect of pregnancy on the carbohydrate tolerance is a factor in the higher incidence of diabetes in married women. This accounts, however, for only part of the difference because diabetes even in married women usually has its onset many years after childbearing has ceased. More important than pregnancy itself would seem to be the effect of overfeeding and underexercise during and after pregnancy. Women usually gain weight during this period, some a considerable amount, and all or a large part of the added weight is often retained. Some indication of this is found in comparing the weights of single and married diabetic women. Among 1326 married women in this group[20] with onset of diabetes after 45, the average weight was 181 pounds, compared to only 161 pounds for 111 single women. No difference, however, was found in the average weights of childless and fertile married women. Another factor in the difference between

the single and married women is the generally better economic status of the married. That means more frequent overnutrition and a greater probability of acquiring diabetes as indicated by the weight figures just quoted. It also means more medical care and a greater probability of correct diagnosis of the disease when it occurs. Moreover, there is greater incentive for a single woman to keep her figure than a married woman. Finally, among single women there is a sizeable proportion who do not marry for reasons of health, most of whom are victims of wasting diseases, and, therefore, underweight.

As for the difference in the frequency of diabetes between married men and women, the extremely rapid increase in the frequency of onset among women in the late forties or fifties reflects the strain on the endocrine system during menopause. Gain in weight is very frequent at this period of life.

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THE "GORDON TEST" FOR HODGKIN'S DISEASE.

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In 1932–33 Gordon[1] reported that an encephalitic syndrome of characteristic pattern developed in rabbits injected intracerebrally with suspensions of lymph glands removed from patients with Hodgkin's disease. He obtained this reaction from 19 of the 20

lymphadenoma cases which he studied. Gland biopsies from 41 patients suffering from a variety of conditions (carcinoma, lymphosarcoma, leukemia, tuberculosis) did not produce this effect in rabbits. Van Rooyen[2] similarly studied 20 cases of Hodgkin's disease. Fifteen of these glands produced a picture of encephalitis in rabbits, whereas 13 non-lymphadenomatous glands were negative.

The nature of the agent responsible for this reaction has not been definitely established. Gordon[1] has suggested that a virus may be involved. Van Rooyen,[2] however, considered the response to be a toxic phenomenon, and felt that the absence of demonstrable immunity, the absence of intracellular inclusions, and the inability to transmit the encephalitis from rabbit to rabbit, constituted strong evidence against any virus as an etiologic agent. Friedemann[3] has shown further that the intracerebral injection of normal splenic tissue, of bone marrow (normal or pathologic) or of normal leukocytes (all from humans) produced in rabbits an encephalitis similar to that described by Gordon after inoculation with lymphadenomatous tissue. He suggested that the encephalitogenic agent in Hodgkin's glands, in normal spleen, in bone marrow and in leukocytes was of the nature of a proteolytic enzyme. A proteolytic enzyme was demonstrated in human spleen, bone marrow and leukocytes by Jochmann and Lochemann[4] in 1908.

The problem of the identity of the Jochmann-Lochemann proteolytic ferment with the encephalitogenic agent found in Hodgkin's disease has been studied further by MacKenzie and Van Rooyen.[5] Their results indicate that there is no relationship between the proteolytic and the encephalitogenic properties of a given gland extract. Experiments directed at this phase of the problem are in progress in this laboratory now and will be discussed in a later communication.

In the reports of Gordon and of Van Rooyen, only Hodgkin's lymph nodes produced an encephalitis in rabbits. Lymph nodes from other diseases did not produce this reaction, although in several instances lymphadenomatous nodes failed to produce it. These reports indicated that the injection of suspensions of Hodgkin's lymph nodes into rabbit brains might serve as a valuable biologic test for the presence of Hodgkin's disease. Manson,[6] however, reports 3 false positive tests; in 2 instances from nodes histologically diagnosed tuberculosis and in 1 node showing simple hyperplasia.

The purpose of this report is to present our experience with the "Gordon test."

Method and Material. *Method.* Lymph nodes obtained by biopsy were sent to the laboratory immediately after removal from the patient. Using sterile technique, the gland was weighed, after as much as possible of the fatty and fibrous tissue had been dissected away. It was then minced with scissors in a mortar, and thoroughly ground up with a pestle. Enough broth was then added to make a

10% suspension. The broth used (both in grinding and diluting) contained 0.5% phenol and its reaction was accurately adjusted to a pH of 7.1.

The gland suspensions were tested for sterility after grinding, and always on the day preceding and on the day of injection into animals. All emulsions were kept in cotton-stoppered tubes in the icebox at 6° C. and injected into animals after from 8 to 10 days of storage. Where the material was adequate in amount, injections into rabbit brains were made 24 hours after preparation of the suspensions. When the results were negative, further inoculations were made in from 15 to 20 days, and in several instances after a longer period of storage.

The rabbits were injected in the manner suggested by Gordon. Under light ether anesthesia, 0.25 cc. of gland suspension was given intracerebrally and from 0.5 to 0.75 cc. intravenously. The animals were examined daily. Temperatures and weights were recorded daily at first. Later the temperature was taken only when the animal showed abnormal signs, and the weights were recorded intermittently as the animals' clinical status changed.

Only definite neurologic changes, such as spasticity, ataxia, tonic fits on stimulation, and delayed flaccid paralysis were accepted as criteria of a positive test. Hyperexcitability and tremor in the first 72 hours after injection were not considered to be significant. At first the animals were observed for 21 days, but later this period was extended to from 30 to 35 days.

Material. Twenty-nine lymph nodes have been studied. Nine came from patients with Hodgkin's disease, as proved by histologic study. The other 20 biopsy specimens were from patients clinically suspected of having Hodgkin's disease, but the histologic examinations did not show Hodgkin's granuloma. A résumé of the individual cases of Hodgkin's disease, including the results of the rabbit tests, follows:

CASE 1. E. V., female, aged 34, was admitted June 7, 1934, for a dermatitis of unknown etiology. She returned 2 months later with swollen cervical glands; leukocytes, 23,600. Biopsy of gland showed histologically typical Hodgkin's granuloma.

Rabbits 103 and 104 were inoculated with a suspension of excised gland which had been stored in the icebox for 9 days. Both animals showed neurologic changes on the 5th or 6th day. Progressive ataxia, spasticity and cachexia developed. Animals killed after a month for histologic study.

CASE 2. M. B., male, aged 48, was admitted November 1, 1934, because of intense abdominal pain of 3 weeks' duration. The significant findings were generalized glandular enlargement, enlarged liver and spleen, and anemia. Biopsy of axillary gland showed histologically typical Hodgkin's disease.

Rabbits 142, 666, 826 and 828 were inoculated with gland suspension stored in the icebox for 3 days. All 4 animals developed signs of an encephalitis.

CASE 3. E. N., female, aged 70, was admitted November 21, 1934, because of weakness of 5 months' duration. A small mass was found in

the left axilla. Biopsy of this mass showed histologically typical Hodgkin's disease.

Rabbits 145 and 146 were inoculated with gland suspension stored in the icebox for 11 days. These animals remained normal. Rabbits 901 and 902 were inoculated with node suspension stored in the icebox for 27 days. Both animals developed encephalitic symptoms characterized by spasticity, ataxia and spastic fits. Both died.

CASE 4. R. B., female, aged 26, for 2 years had swollen glands in the neck. Biopsy during March, 1934, did not establish a diagnosis. The biopsy wound drained for 3 months. In January, 1935, generalized lymphatic enlargement developed. Biopsy of axillary node revealed a histologic picture of which Dr. G. H. Whipple said: "Definitely Hodgkin's disease—but tuberculosis might be present."

Rabbits 162 and 163 were inoculated with node suspension stored in the icebox for 7 days. Both animals developed typical signs of encephalitis on the 4th day. Four guinea pigs inoculated with fresh and stored node material did not show any tuberculosis on autopsy. The guinea pigs were also given skin tests with tuberculin. The reactions were negative.

CASE 5. J. C., male, aged 60, with no reliable history. Material was obtained at autopsy on October 28, 1934. Involved lymph-nodes were obtained from neck, axillæ, and retroperitoneal regions. The spleen, liver and lungs were also involved. All were histologically typical of Hodgkin's disease. Lymphatic tissue and infiltrated tissue from liver and spleen were prepared and stored in the icebox for 17 days. One rabbit was inoculated with suspension from each tissue. All rabbits developed typical signs of encephalitis during the 4th, 5th and 6th days.

CASE 6. P. C., male, aged 7, admitted March 23, 1935, was first seen on May 8, 1930, when a generalized enlargement of lymph-nodes was noted. Biopsy of an inguinal gland was performed on August 1, 1930. Histologically, a diagnosis of subacute lymphadenitis was made with Hodgkin's disease listed as a possibility (Dr. G. H. Whipple). A second biopsy on November 14, 1931, showed a histologic appearance more closely resembling that of Hodgkin's disease. Biopsy on March 27, 1935, demonstrated an appearance histologically typical of Hodgkin's disease.

Rabbits 741 and 744 were inoculated with lymph-node suspension stored in the icebox for 10 days. Both rabbits developed symptoms of encephalitis on the 4th day.

CASE 7. T. M., male, aged 26, for 6 months had intense itching of both wrists; for 2 months, increasing swellings in the neck. Diffuse enlargement of lymph nodes was observed. Biopsy showed typical Hodgkin's

. d NL were inoculated with node suspension which had been stored in the icebox for 16 days. Both animals developed abnormal neurologic signs on the 5th day.

CASE 8. G. G., male, aged 62, admitted on June 2, 1933, for respiratory difficulty. Widening of mediastinal dullness and a generalized lymphadenopathy were present. Biopsy of an axillary gland on September 6, 1933, demonstrated typical Hodgkin's granuloma. A second biopsy on October 27, 1933, also showed Hodgkin's granuloma. Death occurred on November 21, 1933. At autopsy, lesions entirely typical of Hodgkin's disease were found in liver, spleen, kidneys, skin and lymph-nodes.

Nine rabbits were inoculated with material obtained at both biopsies and at autopsy. Dosage and duration of icebox storage were varied. All tests, however, were entirely negative.

CASE 9. J. H., male, aged 39, had enlargement of cervical lymph-nodes, noted in May, 1934. There occurred progressive development of a diffuse lymphadenopathy with intermittent fever. Biopsy on October 9,

1933, showed histologically typical Hodgkin's granuloma. The patient died during February, 1935. The gross and histologic findings at autopsy substantiated the diagnosis of Hodgkin's disease.

Rabbits 641 and 642 were inoculated with lymph-node suspension stored in the icebox for 11 days. Both animals remained normal. Rabbits 643 and 644 received the same suspension after storage in the icebox for 20 days. Both animals remained normal. Material prepared from autopsy specimens also gave negative results on inoculation into 11 rabbits.

Control Material. The biopsy specimens from 20 patients did not show histologic evidence of Hodgkin's granuloma. These node suspensions did not produce neurologic changes in any of the animals injected. A summary of these cases is given in Table 1.

TABLE 1.—CONTROL GROUP.

Patient.	Sex.	Age, yrs.	Clinical diagnosis.	Histologic diagnosis.	Source of gland.	Gordon test.
W. B. 73658	M	41	Pulmonary tuberculosis	Tuberculosis	Axilla	Negative
M. O. 86948	F	30	Glomerulonephritis	Chronic lymphadenitis	Neck	"
E. W. 95140	F	34	Not determined	Chronic lymphadenitis with cystic changes	Mesentery	"
A. G. 87860	M	17	Tuberculous adenitis	Hyperplastic tuberculosis	Neck	"
F. S. 96533	M	61	Lymphatic leukemia	Lymphatic leukemia	Neck	"
C. A. 70606	M	23	Infectious mononucleosis	Chronic lymphadenitis	Neck	"
R. F. 65568	M	21	Infectious mononucleosis	Chronic lymphadenitis	Axilla	"
L. P. 90188	M	20	Chronic nephritis	Hyperplastic node	Neck	"
M. M. 81335	F	33	Tuberculous adenitis	Tuberculosis	Neck	"
B. D. 21540	M	8	Tuberculous adenitis?	Chronic lymphadenitis	Neck	"
V. T. (HH)	F	33	Ulcerative colitis	Chronic lymphadenitis	Mesentery	"
Y. (AOH)	M	25?	Leukemia	Leukemia	Neck	"
P. T. 95426	F	22	Banti syndrome?	Hyperplastic node	Axilla	"
W. M. 100968	M	26	Lymphosarcoma	Lymphosarcoma	Axilla	"
L. C. 99987	F	34	Tuberculous adenitis	Tuberculosis	Neck	"
D. V. 869	M	36	Lues? Tuberculosis?	Hyperplastic node	Axilla	"
C. Z. 1191	F	27	Lymphosarcoma	Lymphosarcoma	Groin	"
A. S. A2888	M	65	Cardiac death	Lymphosarcoma	Retroperitoneum (autopsy)	"
G. D. (RGH)	F	47	Profound anemia—Cause?	Tuberculosis	Neck	"
C. N. 100778	M	15	Not determined	Hyperplastic node	Neck	"

Discussion. Seven of 9 lymphogranulomatous nodes, when inoculated intracerebrally into rabbits, produced an encephalitic syndrome. In 2 instances, where tissue was obtained from histologically established cases of Hodgkin's disease, this reaction was not obtained. From both, biopsy specimens were obtained on 2 occasions, and enough material was available at autopsy to permit making an adequate number of rabbit tests. Dosage and time of icebox storage of the suspensions varied, but all of the inoculated animals remained free of abnormal neurologic manifestations.

Of the control group of 20 lymph nodes, 5 were tuberculous and 2 came from patients with infectious mononucleosis. None of the control glands produced signs of encephalitis on inoculation into rabbits.

The results of our limited series of observations suggest that the "Gordon test" may be of distinct value in the diagnosis of Hodgkin's disease, especially in those instances where the histologic findings are uncertain. A negative test at the present time has no diag-

nostic significance. It is apparent, however, that in order to settle the question of possible "false positive tests," additional cases must be studied.

Summary. 1. Biopsy material from 7 of 9 cases of Hodgkin's disease produced an encephalitic syndrome (a positive "Gordon test") when inoculated intracerebrally into rabbits.

2. Twenty control lymph-nodes, including 5 tuberculous nodes and 2 nodes from infectious mononucleosis were negative.

3. There were no false positive tests. Two of 9 nodes from established cases of Hodgkin's disease failed to give a positive test.

The author wishes to express his thanks to Dr. G. P. Berry and Dr. J. S. Lawrence for interest and help in this work.

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HODGKIN'S DISEASE OF THE LUNG.*

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The material for this report was obtained from a study of 29 patients with a diagnosis of Hodgkin's disease who were admitted to the University of California Hospital from 1928 to 1935. It is our purpose to describe, from our analysis of this material, the clinical, roentgenologic and pathologic manifestations of pulmonary involvement in Hodgkin's disease. We have used data from published reports in the literature for comparison and amplification of our data. Of the 29 cases studied, 9 showed clinical or pathologic

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evidence of pulmonary involvement. Seven of these cases are reported in essential detail.

Incidence. Our search of the literature has revealed the following published statistics of incidence (Table 1). These series are all small, probably on account of rigid diagnostic criteria, including autopsy. Our series appears larger by reason of less rigid criteria, as not all of the patients came to autopsy. The diagnosis in every instance of our 29 cases, however, was carefully checked by biopsy material and histologic study. Although the total number of reported cases is small, and despite the different diagnostic criteria used (clinical or pathologic), it will be noted that the reported statistics agree closely.

TABLE 1.

Author.	Total number cases.	With pulmonary involvement.	Per cent.
Ceelen-Rabinowitsch	10	4	40.0
Herxheimer	8	5	61.0
Sternberg	15	5	33.3
Weinberg	7	2	28.0
Versé	16	6	37.0
Moolten	18	9	50.0
Whitaker	22	7	32.0
Authors	29	9	31.0
Total	125	47	37.6

The report of 7 authors show the incidence of pulmonary involvement to be 40%.

Pathology. The lesion may be primary or secondary. The primary type is very rare, although Moolten[1] includes it in 10% of all cases of pulmonary Hodgkin's disease. The primary forms arise from lymphoid nodules within the lung parenchyma and the submucosa of the bronchi, the so-called submucosal and auxiliary lymphoid tissue.[2] The secondary type most commonly invades the lungs from the bronchomediastinal lymph nodes, but may extend from the thoracic spine, ribs, pleura, pericardium or thymus. Bernard[3] states that a primary origin in the pleura is more common than in the lung.

Versé[4] classifies pulmonary Hodgkin's lesions as follows:

1. Hilus node involvement with direct invasion of lung tissue: (*a*) By direct extension from the lung hilus; (*b*) by breaking through the mediastinal pleura.
2. Hilus node involvement with intra- and peribronchial spread into the lungs.
3. More or less lobar infiltration with various grades of bronchomediastinal involvement.
4. Confluent lobular foci with associated involvement of lymph nodes.
5. Miliary disseminations.

Grossly, the lesions may resemble metastatic tumor nodules,

massive expansive growths, lobar consolidation or miliary disseminations; and numerous cases with cavity formation have been reported.[5–10] Lyon[11] reported a case in which the granuloma had perforated the chest wall.

Histologically, one may find typical granulomatous tissue invading and following peribronchial and perivascular structures, also frequently extending into the interstices and alveoli.

Pleural effusion may occur in association with infiltration of the lung or pleura. Effusion may be due to mechanical factors alone, *i. e.*, pressure upon the great vessels by glandular masses. Serosanguinous, serofibrinous, or even purulent effusions occur, and are usually very cellular. Cases with chylous effusion have been reported. According to Bernard,[3] any effusion which cannot be explained in any other way should lead to suspicion of primary pleural Hodgkin's disease.

Among our patients, using the Versé classification above, we found 1 case corresponding to Type 1, 1 corresponding to Type 5, 2 corresponding to Type 2, 1 each corresponding to Types 3 and 4, and 1 corresponding to a combination of Types 2 and 3.

Symptoms and Signs. The symptoms associated with pulmonary Hodgkin's disease are most frequently cough and dyspnea; less frequently, chest pain, expectoration and hemoptysis. Of 7 patients presented in detail in this report, 6 had dyspnea; 5, cough; and 1, chest pain. Five showed signs of fluid; 2 of these showed signs of consolidation, and 2 showed only scattered râles. Dyspnea of marked degree was a symptom of those patients with extensive pleural effusions, although it was also marked in 3 patients having infiltration of the lung without the presence of fluid. Cough, usually unproductive, occurred in all patients showing parenchymatous lesions. Chest pain was a striking symptom in 1 case. In another patient, cough was the predominant symptom before infiltration of the parenchyma had occurred. Two patients had respiratory symptoms at the onset of the disease. In 1 of these, cough was the symptom first prompting the patient to seek medical advice. In the other 5 patients the respiratory symptoms appeared 5 months, $2\frac{1}{2}$ years, 3 years, 3 years and 9 months, and 8 years after the onset of lesions elsewhere in the body.

Roentgenologic Findings. There is no characteristic Roentgen picture of pulmonary Hodgkin's disease. If the film reveals miliary disseminations, or infiltration or cavitation of the upper lobes, tuberculosis is suggested. If the shadows resemble metastatic nodules or large expanding tumors, carcinoma is suggested and may be the diagnosis made. In 1 of our cases the early Roentgen diagnosis was tuberculosis, while in another it was metastatic carcinoma.

In the majority of cases where there is evidence of Hodgkin's disease elsewhere in the body, the Roentgen findings will establish

the diagnosis of pulmonary involvement. The difficulty in these cases is the possible coëxistence of pulmonary tuberculosis. We have not found this association to be common, either in our own cases or in reports from the literature.

The greatest difficulty presents itself in those cases where the primary lesion is in the lungs. Here tuberculosis, lymphosarcoma, carcinoma, or chronic pneumonitis may give similar pictures. Many roentgenologists believe that tuberculosis and carcinoma can be fairly sharply differentiated from lesions due to Hodgkin's disease. Whitaker[12] lays stress upon the sharper outlines of sarcomatous and carcinomatous lesions. Wessler and Greene[13] stress the enlargement of paratracheal nodes in Hodgkin's infiltration. The response to Roentgen ray treatment may be of help in the differential diagnosis.[14,15,16] Tuberculosis will show no response. Carcinoma responds slowly, if at all. On the other hand, the lesions of Hodgkin's disease and lymphosarcoma should regress rapidly. It is stated by some authors that lymphosarcoma will show a more rapid rate of regression than Hodgkin's lesions, but this depends to a large extent upon the relative degree of cellularity and fibrosis of the lesion. It should be stated that there are investigators who believe that radiation does not cause satisfactory regression of Hodgkin's lesions in lung parenchyma. For this reason the response to radiation may not be of much help as an aid in differential diagnosis.

Prognosis. We were unable to determine any definite connection between the time of onset of the pulmonary symptoms and the time of death (Table 2). This may be due in part to the variable interval between the appearance of the lesion and the onset of symptoms. Moreover, there is no definite relationship between the extent of the lesion and the symptomatology. If pleural effusion occurs early, the symptoms are marked, whereas it has been noted that extensive infiltration of the lung parenchyma may exist without symptoms pointing to the chest.

TABLE 2.

Case No.	Time of appearance of chest symptoms after onset of disease.	Length of life after onset of pulmonary involvement.
1	2 years, 6 months	2 months.
2	5 months	Subsequent course not known.
3	8 years	2 years, 3 months.
4	Primary symptoms	4 years, 3 months.
5	3 years	3 months.
6	3 years, 9 months	1 year, 9 months.
7	With onset of disease	1 year, 4 months.

Case Reports. CASE 1.—M. W., male, aged 22, entered the hospital May 5, 1933. The chief complaints were weakness, diarrhea, loss of weight and swelling of glands in the neck. Two and a half years prior to entry, following tonsillectomy, he had noted swelling of the left side of the neck. In July, 1931, glands were removed from the neck, followed by

Roentgenotherapy. Progressive weakness and loss of weight supervened with intermittent periods of diarrhea, which lasted until the present entry. Two weeks prior to entry he began to have a non-productive cough. Physical examination showed: Respirations, 35 per minute; occasional sonorous râles in the left interscapular region. For 2 days following admission the patient was very dyspneic. On May 9, the possibility of emphysema was considered. During his stay in the hospital, he suffered from intermittent [illegible] which could not be accounted for by the chest findings. [illegible] râles were heard. The respirations ranged from 30 to 60 a minute. A Roentgen film, taken June 3, showed diffuse parenchymatous shadows throughout the right lung field, and to a lesser extent in the left lung field (Fig. 1). The patient was discharged on June 6. Death occurred in July, 1933. No necropsy.

CASE 2.—R. B., female, aged 37, was admitted, July 17, 1933, with weakness, loss of weight, dyspnea, intermittent fever and swelling in the neck. Her first symptoms appeared in August, 1932, and consisted of left temporal headache, itching of the skin and rash. This condition cleared up and the patient felt well until January, 1933. Following an attack of influenza she complained of dyspnea, a loss of 25 pounds in weight, and intermittent fever. In March, 1933, she noted swelling on the right side of the neck, followed by swelling of the left side of the neck and in the axillæ and groins. She had also noted excessive pigmentation on her body for 2 months. Just prior to admission, dyspnea was the most annoying symptom. Physical examination showed: Brownish pigmentation of the face and arms. Large masses of discrete and confluent, slightly tender glands in the cervical, axillary and inguinal regions. Chest examination showed diminished mobility of the left side; dullness over the left base posteriorly. Breath sounds at the right apex posteriorly were high-pitched and bronchial. Numerous fine, subcrepitant râles were heard throughout. The spleen and liver were palpable. There was pitting edema of both ankles, and fluid in the abdomen. The pupils were fixed and reacted sluggishly to light; knee jerks were diminished. Kahn test, 4+. A roentgenogram of the chest taken, July 18, 1933, showed scattered area of density through both lower lobes and the left upper lobe (Fig. 2). She received five courses of deep Roentgen therapy to the chest. Following irradiation there appeared to be clinical improvement in her chest condition. She was discharged, July 29, 1933, and returned to her physician. Her course since discharge is not known.

LEGENDS FOR FIGS. 1 TO 11.

FIG. 1.—Diffuse parenchymatous involvement of the right lung. Lesser involvement of the left lung.

FIG. 2.—Scattered areas of density through both lower lobes and left upper lobe.

FIG. 3.—Large collection of fluid at right base. Small collection at left base.

FIG. 4.—Perivascular infiltration with lymphogranulomatous lesion extending into lung parenchyma.

FIG. 5.—Diffuse shadows extending throughout both lung fields.

FIG. 6.—Circumscribed nodule of lymphogranulomatous tissue.

FIG. 7.—Fluid level in the left chest extending to the third rib.

FIG. 8.—Large smooth shadow in the region of the left hilus.

FIG. 9.—Mediastinum clear. Infiltrating lesion extending down to base of right lung.

FIG. 10.—Increased peribronchial shadows producing increased linear shadows throughout the left lung field. Density at the right base.

FIG. 11.—Peribronchial infiltration. Marked fibrosis in lower part of field.



FIG. 1



FIG. 2



FIG. 3



FIG. 5



FIG. 4



FIG. 6



FIG. 7

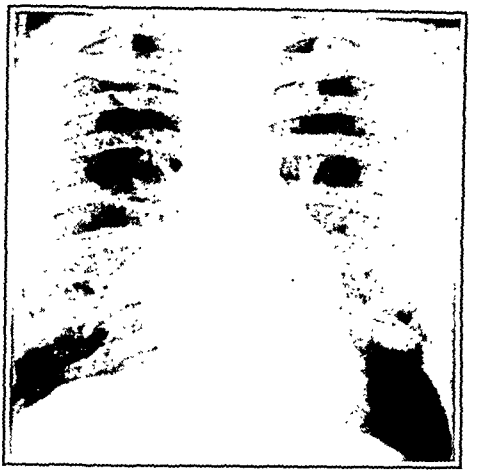


FIG. 8

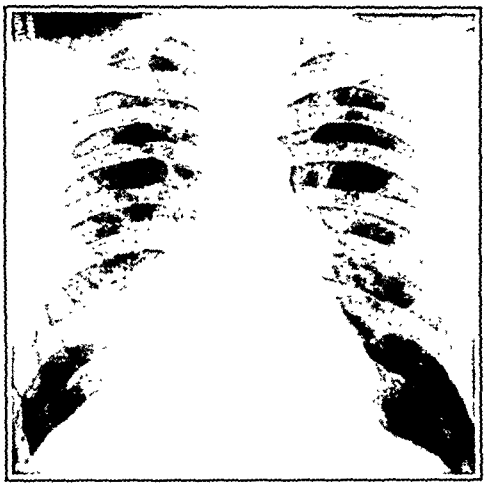


FIG. 9



FIG. 10



FIG. 11

CASE 3.—R. F., male, aged 56, was admitted, July 20, 1931, complaining of dyspnea of 2 years' duration. Ten years before, he had noted swelling of the neck. A gland was removed and a histologic diagnosis of Hodgkin's disease was made. In 1927, he had had some Roentgenotherapy. For several years he had nocturnal attacks of orthopnea. Physical examination on admission showed signs of bilateral pleural effusion. Fourteen hundred cc. of clear yellow fluid were removed from both sides. Five days later, 1850 cc. of fluid were removed from the right side. Chest films taken on July 28 showed a large collection of fluid at right base and a small collection on the left (Fig. 3). He received 2 Roentgen ray treatments to the chest, following which there was no improvement in the patient's symptoms. Death occurred on October 9, 1931. At necropsy, the left pleural cavity contained 5000 cc., and the right pleural cavity 4000 cc. of seropurulent fluid. The lungs were normal in weight. There were small, white foci scattered over the pleural surface. No other gross lesions were noted. Microscopic examination of the lungs showed small areas of perivascular cellular infiltration. The cells consisted of lymphocytes, endothelial cells and occasional giant cells. There were no eosinophils. No fibrosis (Fig. 4).

CASE 4.—L. P., male, aged 30, was seen in consultation with Dr. Alexander Bartlett, of San Francisco, by one of us (E. H. F.). In December, 1928, the patient was thought to be suffering from arthritis of the upper spine. In March, 1929, he developed a cough; and a chest plate taken at that time showed enlarged mediastinal shadows. From 1930 to 1931, he received periodical Roentgenotherapy to the chest. He was admitted to the hospital on December 8, 1931. Physical examination showed enlarged glands in the axillæ. There was some impairment of the percussion note and breath sounds over the left side of the chest. A chest film taken, December 11, showed 2 circumscribed, rounded nodules in the left lower lobe. A diagnosis of metastatic carcinoma was made. A course of Roentgenotherapy was given and he was discharged on December 16, 1931. On December 26, he was readmitted, receiving another course of deep Roentgenotherapy. On January 2, 1932, he was discharged with no apparent change in his condition since the first entry. On January 23, 1932, he was again admitted. Between the present and previous entries he had been confined to bed because of severe dyspnea. Three days before admission, 2500 cc. of greenish fluid were removed from the right pleural cavity. On January 26, 1800 cc. of greenish fluid were removed. Culture showed no growth. Pathologic examination of the cellular material from the fluid gave findings consistent with Hodgkin's disease. A chest film taken at this time showed diffuse shadows extending through both lung fields (Fig. 6). On January 28, histologic examination was made of a gland removed from the axilla; the diagnosis was Hodgkin's disease. The patient's dyspnea was so extreme that after repeated tappings the possibility of a bronchial stenosis was entertained. Bronchoscopy, however, showed no obstruction. Death occurred on March 18, 1932. Necropsy showed the right pleural cavity to be filled with blood-stained fluid. The right lung was collapsed and adherent on the anterior and posterior surfaces. It contained scattered areas of nodular consolidation, varying in size from 0.5 to 3 cm. The mediastinum was completely filled with similar nodules. The left pleural cavity contained 800 cc. of clear, yellow fluid. The left lung was studded with firm nodules similar to those seen in the right lung. Microscopic examination showed marked congestion and edema. There were very large circumscribed areas in which the lung architecture was completely lost. Practically no alveolar structure was made out. In some places only a dense hyalinized fibrosis was present. In others, fibrosis was less marked and showed a cellular infiltration, while in still others a cellular infiltrate predominated. The infiltration exhibited marked

pleomorphism and consisted of lymphocytes, endothelial cells, giant cells and occasional eosinophils. The giant cells were mononuclear and multinuclear. In some the nuclei were arranged about the periphery, while in others they had a central arrangement. The nuclei were hyperchromatic. A few mitoses were noted (Fig. 6).

CASE 5.—C. R., male, aged 49, in November, 1931, noted swelling of the neck. In April, 1932, a diagnosis of Hodgkin's disease was made by histologic examination of a gland. A chest film taken, May 19, showed a few dense parenchymatous shadows of small size in the right upper lobe. Between April and July, 1932, he was given 10 Roentgen ray treatments. In August, he was admitted to the hospital complaining of pressure on the throat, interfering with breathing and swallowing. He also complained of sharp pain in the left side of the chest associated with dyspnea, and an unproductive cough which had been present for 3 weeks. Physical examination showed signs of fluid in the left pleural cavity, extending to the level of the third rib (Fig. 7). On August 6, 2000 cc. of clear, yellow fluid were removed from the left pleural cavity. On August 11, a chest film showed widening of the mediastinum above the aorta and peribronchial infiltration in the left lower lobe (Fig. 10). On this admission, cutaneous nodules were found which histologic examination proved to be lesions of Hodgkin's disease. Death occurred on October 6, 1933.

CASE 6.—W. M., male, aged 36, in August, 1928, complained of itching. In January, 1929, examination disclosed a typical urticarial rash and some enlarged lymph nodes in the right supraclavicular region. In February, 1929, a diagnosis of Hodgkin's disease was made from histologic examination of a lymph node. A Roentgen film, taken April 2, 1930, showed a large, smooth shadow in the region of the left hilus (Fig. 8). He had several courses of Roentgenotherapy. In June, 1930, an enlarged gland was found in the left axilla. In September, small, shotty glands appeared in the anterior triangle of the left side of the neck. In April, 1931, he first began to cough. A Roentgen film, taken September 3, showed an infiltrating lesion extending from the right hilus to the base of the right lung (Fig. 9). In November, thoracentesis of the right chest was performed and 1500 cc. of serosanguineous fluid removed. This was repeated several times before death occurred, in January, 1932.

CASE 7.—H. V., male, aged 25, in April, 1933, noted a dull, aching pain across the lower back. At the same time glandular enlargements appeared in the neck, axillæ and groins. This was followed by fever, anorexia, malaise and loss of weight. Since the onset of the illness, he has had dyspnea and productive cough. He was admitted to the hospital on March 1, 1934. Physical examination showed the presence of fluid in both pleural cavities. A Roentgen film taken on March 2 showed increased density in the peribronchial structures leading from the left hilus to the base. Thoracentesis was performed on March 15. A clear, yellow fluid was obtained. A pleural friction rub was heard in the right lower axilla on March 20. On April 10, the patient complained of precordial pain, and a pericardial friction rub was elicited. Five doses of [illegible] were given over the chest. The patient was discharged [illegible]. He was readmitted, May 29, with nausea and vomiting, marked dyspnea, productive cough and pain across the front of the chest. Physical examination showed signs of fluid at both bases, with displacement of the mediastinum to the right. From May until August, repeated thoracenteses were performed and large amounts of serosanguineous fluid withdrawn. A chest film, taken August 2, 1934, showed increased peribronchial shadows throughout the left lung (Fig. 10). The condition was aggravated by marked abdominal ascites, a failing heart and renal insufficiency. Death occurred on August 25, 1934. Necropsy findings: Pleural cavities were

filled with thin grayish fluid which compressed the lungs until they occupied about one-fourth of the chest cavity. There were a few filmy adhesions at the left apex and at the right base posteriorly. The parietal pleura was studded with white nodular infiltrations. The bronchomediastinal nodes were enlarged, and on cut section showed fibrosis and occasional hyperplastic, glandular areas. Both lungs were markedly compressed. The right weighed 380 gm. and the left 410. There were many small, rounded, yellow nodules in the parenchyma of the left lung, particularly in the bronchial regions. The right lung showed a small area of atelectasis at the base. Microscopic examination showed peribronchial, and to a lesser extent perivascular, fibrosis. These fibrosed areas contained numerous lymphocytes, neutrophils, eosinophils and reticular cells. Occasional Sternberg-Reed cells were found (Fig. 11).

Summary. The conclusions from our studies are in accordance with those of other students of this disease who have been interested in the incidence of pulmonary involvement. If 37.6%, which is an approximate incidence of pulmonary involvement as shown by Table 1, should hold in larger series, then pulmonary Hodgkin's disease is not rare. The ratio of pulmonary involvement to the total number of cases of Hodgkin's disease would actually work out to be relatively high.

Five of the 7 cases showed pleural effusion. This is 71%, which is somewhat higher than one would expect to find in a larger series of cases. Three of these cases with pleural effusion showed pleural lesions, due to Hodgkin's granuloma, at autopsy. We were unable to form an adequate idea, from our small series of patients, of the average tenure of life after pulmonary involvement is definitely ascertained.

We are preparing a report, to follow this study, dealing with pulmonary involvement in patients with lymphosarcoma and leukemia. This should prove interesting from the standpoint of comparison.

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PLASMA CELL LEUKEMIA.

A Consideration of the Literature With the Report of a Case.

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Although more than 400[1] cases of plasmacytoma* have been recorded in the literature, the finding of plasma cells in the peripheral blood in this disease seldom has been mentioned. Aschoff,[2] in 1906, was the first to describe such a condition. Lindh-Muller and McNaughton,[3] in 1931, reviewed 6 reports of plasmacytoma with the blood picture of plasma cell leukemia and added observations on 2 more cases. In 1934[4] Osgood reported such a case, and another has been recorded recently at the Massachusetts General Hospital.[5] Thus, of a total number of 11 cases, 4 have been observed in this community during the past 4 years. Whereas it is a rare condition, we venture to predict that the disease occurs more often than commonly is appreciated. Since it is readily diagnosed when suspected, it has seemed worthwhile reporting an additional case of plasmacytoma with a blood picture of plasma cell leukemia.

* The term plasmacytoma is used to express plasma cell tumors described by the names of plasmoma and multiple myeloma.

Case Report. An American housewife of 60 entered the hospital in December, 1934, complaining of pain in the right chest. Except for chronic constipation she had always been in robust health. During the previous year she had tired easily and had suffered fleeting pains in the back and shoulders. For about 8 weeks she had experienced recurrent pains, first in the right and later in the left chest, which recently had become so sharp and constant that she took to bed. Deep breathing or change of posture in any direction intensified her discomfort. Because of the pains, failing strength and loss of appetite she sought medical care.

On examination, this gray-haired woman appeared to be pale and tired. The breathing was shallow but not labored. Over the shoulders and upper thorax anteriorly several purpuric spots were visible. No bone tenderness was elicited. The pupils, fundi, and scleræ of the eyes were normal. The teeth were carious. The tongue was coated and dry. There was no palpable lymph node enlargement. Percussion resonance was somewhat impaired over the right lower thorax. Spotty areas with bronchial breath sounds and diffusely scattered moist râles were heard in both lungs. Except for a soft systolic murmur at the mitral valve area, the heart sounds were not abnormal. The blood pressure was 160 systolic, 80 diastolic. Examination of the abdomen, pelvis and rectum revealed no abnormality. Reflexes were normal.

The initial blood counts were: red blood cells, 3,130,000 per cmm.; white blood cells, 21,800; hemoglobin (Sahli), 63%. On discovering 27% plasma cells in the blood smear, a diagnosis of plasmacytoma was suggested and roentgenograms were taken. They were reported as follows:

Thorax. Cloudy density lower half right lung field.

Lumbodorsal Spine. Osteoporosis with wedge-shaped deformity of the tenth and twelfth dorsal and of the first lumbar vertebræ.

Skull. Many small punctate holes in the left lateral aspect of skull.

TABLE 1.—BLOOD FINDINGS IN CASE OF PLASMA CELL LEUKEMIA.

Date.	R. B. C. per cmm.	Hgb., %.	W. B. C. per cmm.	Differential leukocyte count, %.							
				Neutrophils.	Lymphocytes.	Atypical plasma cells.	Plasma cells.	Monocytes.	Eosinophils.	Basophils.	Myelocytes.
12/28/34 . .	3,130,000	63	21,800	47.5	22.0	3.0	24	2.5	1.0	0.0	0.0
1/ 2/35 . .	2,725,000	56	17,000	50.0	24.0	2.0	18	3.0	2.5	0.0	0.5
1/ 4/35 . .	2,830,000	57	14,150	36.5	22.5	6.5	24	3.5	3.5	0.0	3.5
1/ 9/35 . .	1,960,000	50	21,000	52.0	19.5	8.0	12	4.0	1.0	0.5	3.0
1/11/35 . .		..	50,150	34.0	19.5	10.0	33	2.0	0.0	0.0	1.5

Laboratory Findings. Of chief interest were the blood counts listed in Table 1. The hematocrit indices of the red cells were essentially normal. The platelets were reduced in number. The urine contained a large trace of albumin and frequently showed Bence-Jones' protein. The urine sediment consisted of a few red blood cells, white blood cells and granular casts.

The calcium and phosphorus contents of the blood were normal. The non-protein nitrogen of the blood varied from 60 to 76 mg. on three determinations. The total proteins of blood serum varied from 11.3 to 11.9 gm. per 100 cc.; the albumin fraction from 2.87 to 3.2 gm.; the globulin fraction from 7.75 to 8.8 gm.; while the fibrin content remained normal. The blood Kahn reaction was negative.

Course. During her stay in the hospital the patient became progressively weaker. An initial temperature of 102° F. subsided to normal on the second day, where it remained for 2 weeks. The pulse varied from 80 to

90 beats per minute. On the 7th day many new purpuric spots appeared over the thorax, back and forearms. On the 12th day there was blood oozing from the nose and gums. The signs referable to the lungs remained those of bronchopneumonia. The spleen and liver were not palpable. On the 14th day the temperature mounted suddenly to 102° F., and the patient became comatose and died. The clinical diagnoses were: plasmacytoma; plasma cell leukemia; bronchopneumonia.

Postmortem Examination. The body was that of a well developed, fairly well nourished elderly white woman. Ecchymotic areas of varying size were seen in the skin over the left hand and wrist, thighs, left groin and over both pectoral regions. The serous cavities were not remarkable except for firm fibrous adhesions at both lung apices and at the midportion of the right lung. The heart showed no gross abnormality. Over both pleuræ were seen a number of scattered elevated gray-white nodules 1 to 2 mm. in diameter, surrounded by a dark hemorrhagic zone. The cut surface of the lungs suggested the changes of bronchopneumonia.

The spleen was moderately enlarged, weighing 325 gm., and increased in consistence. The gastro-intestinal tract was normal except for a few scattered submucous petechiæ. In the tail of the pancreas was a soft, reddish-brown nodule 1.5 cm. in diameter. The liver weighed 1450 gm. and showed no gross changes. The kidneys weighed 300 gm. and were pale brownish-gray with a few hemorrhagic areas in the pyramids and cortex. The cancellous bone of sternum, ribs and vertebræ was thin and soft. There were no circumscribed tumor masses. The bone marrow in these areas was soft and reddish-brown. The tibial marrow contained yellow fat tissue.

Microscopic examination revealed no important changes in the heart or lungs. There was diffuse infiltration with plasma-like cells in the spleen and the liver, both in sinusoids and periportal areas. This also occurred in the kidneys, particularly in the interstitial tissue as well as in the pelvis and peripelvic fat, the abdominal lymph nodes, and in the bone marrow of the sternum, ribs, vertebræ and femurs. In the nodule in the tail of the pancreas was found a collection of plasma cells which were seen to invade the adjacent normal tissue.

The pathologic diagnoses were: (1) Findings consistent with multiple myeloma involving sternum, ribs, vertebræ and femur; (2) plasma cell leukemia; (3) plasmacytoma of the pancreas; (4) pyelonephritis; (5) bronchopneumonia.

Discussion. One essential criterion for the diagnosis of plasma cell leukemia is the constant finding of plasma cells in the blood. These are oval or round cells whose characteristic nucleus is identified by its eccentricity, a nucleolus, dense wedge-shaped chromatin masses along the nuclear membrane and a perinuclear pale area. The cytoplasm is basophilic and it may be finely granular or, if degenerated, vacuolar and foamy. In plasma cell leukemia not all cells correspond to this mature type. There also may be cells with centrally located nuclei and some forms barely distinguishable from lymphocytes.

Plasma cells appear in the blood stream in rubeola and rubella, and a few such cells are noted sporadically in other conditions as "myeloma" without leukemia, myeloid leukemia, metastatic carcinoma, and Hodgkin's disease. However, the persistent presence of a considerable number of such cells in the blood of an adult

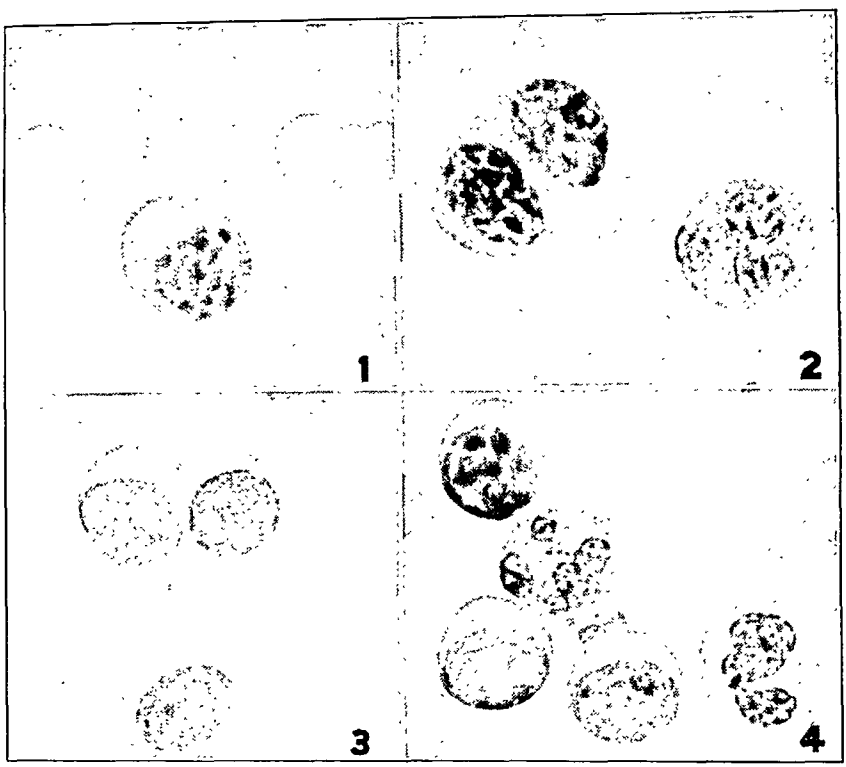


FIG. 1.—Photomicrographs of plasma cells with polynuclears from the patient's blood before death. 1, Typical plasma cell with eccentric nucleus containing nucleolus and heavy chromatin masses (× 1800). 2, Binuclear plasma cell and neutrophil (× 1100). 3, Young plasma cells whose nuclei are less coarsely fragmented—less typical than Fig. 1 (1) (× 1100). 4, Three plasma cells and two neutrophils. The single plasma cell in upper left field shows chromatin clumping. The nuclei of the other two cells, however, are more homogeneous in texture, resembling young lymphocytes (× 1100).

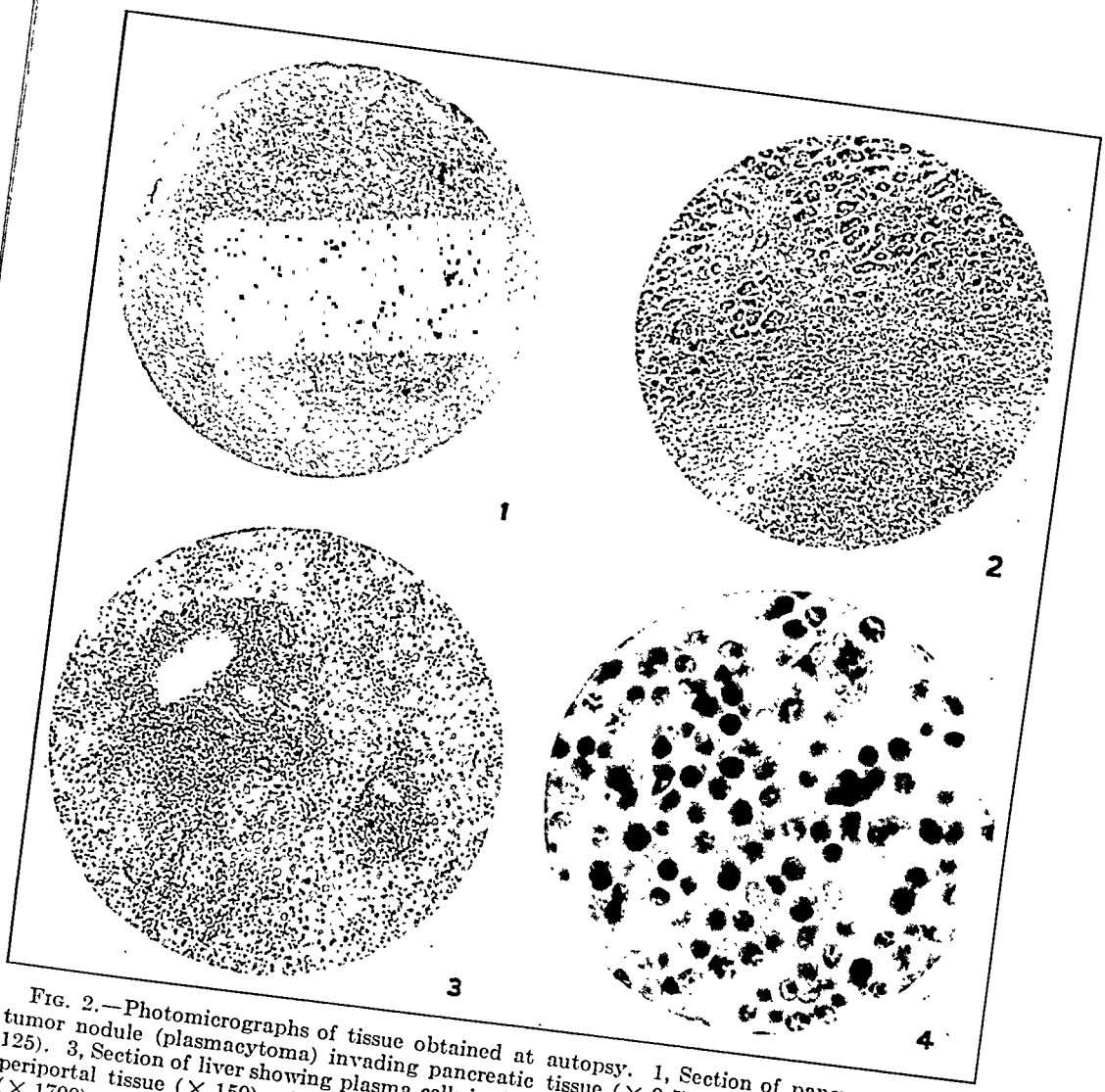


FIG. 2.—Photomicrographs of tissue obtained at autopsy. 1, Section of pancreas showing tumor nodule (plasmacytoma) invading pancreatic tissue (× 9.5). 2, The same section (× 125). 3, Section of liver showing plasma cells in the sinusoids, about the central vein and in the periportal tissue (× 150). 4, Section of vertebral bone marrow, showing many plasma cells (× 1700).

person with the clinical picture of chronic disease is practically pathognomonic of the presence of plasmacytoma with plasma cell leukemia. In the case presented in this report provisional diagnosis was made from study of the blood smears, later to be confirmed by roentgenograms, Bence-Jones proteinuria, and high serum protein.

Exception may be taken to the term "leukemia" for this disease since the number of plasma cells in the blood is not very large and since the total white blood cell count, with few exceptions, is no higher than that occurring with moderate leukocytosis. However, the same may be true of myeloid leukemia. The term "leukemia" in these cases is justified since the condition is essentially a disease of the blood associated with changes in the spleen, liver, bone marrow and lymph nodes and characterized by a diffuse infiltration of the cell type throughout the body. Moreover, the clinical course of these cases resembles the course of other types of leukemia.

In Tables 2 and 3 are grouped the significant data of the reported cases of plasma cell leukemia. All of these exhibited diffuse infiltration of the type cell but few had impressively elevated white blood cell counts. Case 1 of Ghon and Roman[7] was included to illustrate what might be called "aleukemic plasma cell lymphadenosis." Other cases of this type have been recorded.[13, 14, 15] In several cases[6–9] the white blood cell rise and the appearance of plasma cells occurred only a few days or hours before death, as if it were an agonal expulsion of such cells. These episodes may be considered to represent a leukemic phase of leukemia which, through its early course, had been aleukemic. In 4 cases there were associated multiple myelomata;[3, 5, 6, 9] in our case an extraosseous plasmacytoma; in 6 other cases[2, 4, 7, 8, 10, 11] no associated tumors were found at autopsy.

Piney[10] and Osgood[4] emphasized the peculiarity of their cases as being instances solely of plasma cell leukemia because of the lack of associated tumor and of Bence-Jones proteinuria. However, this seems to us a needless academic nicety. The diffuse infiltration throughout the body with plasma cells occurring in the other reported cases warranted the diagnosis of leukemia whether there was an associated tumor or not. Moreover, in this disease, unless meticulously complete Roentgen ray study and search at autopsy for plasmacytoma are made, one may not confidently exclude the presence of "tumors." In neither Piney's nor Osgood's reports were such examinations available. Since Bence-Jones' proteinuria occurs in about 60% of the cases of plasmacytoma and since it occurs in other affections of bone marrow such as myeloid leukemia and metastatic carcinoma, its presence is merely confirmatory and not diagnostic of plasmacytoma (multiple myeloma). Certainly its absence is no criterion for the diagnosis of plasma cell leukemia as those authors contended. In our case Bence-Jones' proteinuria was present on some days and absent on others. It is not generally

TABLE 2.—CLINICAL FINDINGS IN REPORTED CASES OF PLASMA CELL LEUKEMIA.

Case	Age	Sex	Duration of illness	Complications.	R. B. C. per cmm.	Hgb., %	Platelets.	W. B. C. per cmm.	Plasma cells, %	Bence-Jones proteinuria.	Roentgen ray signs of bone changes.
Aschoff, 1906	56	M	6 months	Nephritis; cystitis	2,700,000 to 680,000	50 to 15	Decreased	7600 to 39,000	Present in autopsy blood		
Gluzinski, 1906	47	M	10 months	Bronchitis	3,750,000	61		13,000	Persistent 6 months; peak at 77	Positive	
Ghon and Roman, 1913	72	F	3 weeks	Tbc. pleurisy; ?syphilis	2,500,000		Decreased	5600 to 6200	2 Türck forms		
Hertz and Mamrot, 1913	55	M	3 years	Pericarditis; pleuritis	2,900,000	37		2900 to 19,400	15		
Beck and McCleary, 1919	32	M	5 months	Ascites	2,200,000			8800	5 (1 count before death)	Negative	
Piney, 1924	55	M	5 years	Pneumonia; nephritis	2,660,000	42		8900 to 20,000	6.6 (1 count before death)	Positive	
Muller and McNaughton, 1931	48	M	6 weeks		1,200,000 to 2,200,000	75 to 41	Decreased	11,600 to 27,000	14 to 41	Negative	
Piney and Riach, 1931	38	F	8 months	Bronchopneumonia; cystitis	4,700,000	80	Decreased	50,000 to 60,000	39 to 53		Positive
Osgood and Hunter, 1934	46	F	9 months	Fractured spine	3,360,000	47		23,000 to 42,000	65 (1 count)	Positive	Positive
Cabot case Report 1935	56	M	8 months	Nephritis	1,400,000	30	Decreased	16,600 to 24,000	16 to 33		
	49	M	6 months		2,140,000	55	Increased	18,000	45 to 54	Negative	Positive
	61	F	1 year	Pulmonary infarct; nephritis					5 to 13	Positive	Positive

In the last 2 cases in which serum proteins were studied, the serum proteins were elevated.

TABLE 3.—AUTOPSY FINDINGS IN REPORTED CASES OF PLASMA CELL LEUKEMIA.

Case reports.	Liver.	Spleen.	Bone marrow.	Lymph nodes.	Miscellaneous data.
Aschoff, 1906	Not remarkable	Normal size infiltrated	Diffuse infiltration; no tumor masses	Not enlarged	Nephritis.
Gluzinski, 1906	Infiltrated	Enlarged, infiltrated	Diffuse infiltration and tumor masses	Enlarged, infiltrated	Kidneys infiltrated.
Ghon and Roman, 1913, Case I	Enlarged, infiltrated	Enlarged, infiltrated	Gray, red infiltrated; no tumor masses	Enlarged, infiltrated	Tonsils infiltrated.
Case II	Enlarged, infiltrated	Enlarged, infiltrated	Gray, red infiltrated; no tumor masses	Enlarged, infiltrated	
Hertz and Mamrot, 1913	Enlarged, infiltrated	Enlarged, infiltrated	Not examined	Cervical nodes enlarged	Chronic diffuse nephritis.
Beck and McCleary, 1919	Plasma cells in sinusoids	Not mentioned	Tumor masses in ribs, sternum and clavicles; no diffuse infiltration	Cervical node enlarged and infiltrated	Kidneys infiltrated.
Piney, 1924	Enlarged, infiltrated	Slightly enlarged	White, firm; diffuse infiltration; no tumor masses	Slightly enlarged and infiltrated	Kidneys infiltrated.
Muller and McNaughton, 1931	Slightly enlarged, infiltrated	Enlarged, infiltrated	Diffuse infiltration and tumor masses	Infiltrated	Kidneys, skin, prostate and parotids infiltrated.
Piney and Riach, 1931	Enlarged, infiltrated	Enlarged	Diffuse infiltration; no tumor masses	Peri-portal nodes enlarged; infiltrated	
Osgood and Hunter, 1934	Enlarged, infiltrated	Enlarged, infiltrated	Rib diffusely infiltrated; no palpable tumor mass; incomplete autopsy	Uninvolved	
Cabot case, 1935	?Size; uninvolved	?Size; infiltrated	Diffuse infiltration and tumor masses		

appreciated that one or two examinations are insufficient, and that marked fluctuations in this test may occur during 24 hours.

The finding of both plasmacytoma and leukemia in the case now reported appears to confirm the theory advanced by Lubarsch[12] and Pappenheim,[16] emphasized by Ghon and Roman and others, and reiterated by Jackson, Parker and Bethea[17] that there are comparable gradations in plasma cell tumors analogous to lymphomata. Thus there may be single and benign or multiple and relatively malignant plasma cell tumors. There may be a diffuse cellular infiltration throughout the body, and this in turn may proceed with or without changes in the peripheral blood stream. Moreover, as in certain of the reported instances, several forms may coëxist.

We wish to reassert the desirability of regarding this plasma cell tumor (plasmacytoma) as a pathologic entity whose different forms are not distinct diseases, but are simply gradations in extent and activity of the same disease process.

Summary. A case of plasmacytoma with plasma cell leukemia is reported together with a brief analysis of 11 such cases recorded in the literature.

It is believed that the plasma cell tumor should be regarded as a pathologic entity whose different forms are simply gradations in extent and activity of the same disease process.

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THE EFFECT OF ROENTGEN RAY IRRADIATION ON PLATELET PRODUCTION IN PATIENTS WITH ESSENTIAL THROMBOCYTOPENIC PURPURA HÆMORRHAGICA.*†

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Bleeding in idiopathic purpura hæmorrhagica has long been known to be accompanied by thrombocytopenia.[1, 2] When the blood platelets become reduced to a sufficiently low level, capillary hemorrhages appear in the skin following slight trauma or venous stasis, the bleeding time is increased, and there is a failure of the clot to retract. Since it is generally accepted that the blood platelets play an important rôle in thrombus formation and clotting, this deficiency, in addition to increased fragility of the capillaries, is used as a possible explanation for the development of purpura. There is little to be found in the medical literature, however, on the favorable influence of therapeutic procedures on platelet production in this disease. Kaznelson[3] demonstrated in 1916 a thrombocytosis following splenectomy. Since then, drugs, some possibly of minor importance, which have been employed with supposedly beneficial results, are foreign protein-shock therapy, liver extract, both by mouth and parenterally, iron, ergot, snake venom,[4, 5] ascorbic acid[6] and many others. Remarkably few studies, however, have been reported on the effect of Roentgen ray radiation on the number of circulating blood platelets in idiopathic thrombocytopenic purpura. Bucky and Guggenheimer[7] claim to have demonstrated a rise in blood platelets following stimulative doses of Roentgen ray over the spleen. Other reports[8, 9] do not contain actual platelet counts, but present evidence showing cessation of hemorrhage in patients for varying periods of time after radiation, and thus lend support to the value of this form of therapy. Marzullo,[10] on the contrary, failed to find significant clinical improvement in his patients after Roentgen ray therapy and stated that in 1, notwith-

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† Read before the American Society for Clinical Investigation, Atlantic City, May 6, 1935.

standing cessation of hemorrhage, the platelets did not rise above 100,000 per c.mm. In addition, the recent reports of various authors[11,12,13] on the treatment of purpura hæmorrhagic omit any discussion on the effect of Roentgen ray radiation. In view of the fact that there has been some controversy over the efficacy of Roentgen ray treatment on patients with idiopathic purpura hæmorrhagica, and since the platelet deficiency is of considerable importance in the causation of hemorrhage, it seemed to us desirable to make a careful estimation of the platelets in the circulating blood of patients with this disease before and after the administration of a known Roentgen ray dosage.

Method of Study.—Seven patients, 4 females and 3 males, varying in age from 4 to 67 years, comprised the series for this study. The criteria used in the diagnosis of purpura hæmorrhagica were the spontaneous appearance of petechial hemorrhages and ecchymoses in the skin; an increased capillary fragility; prolonged bleeding after puncture of the lobe of the ear; a failure of the clot to retract; and a marked reduction in the number of platelets. The patients could be divided into 3 groups, depending upon duration and severity of symptoms. Four of the patients had acute recurring thrombocytopenia with purpuric symptoms, 2 had chronic thrombocytopenia with recurring purpura and 1 patient had an acute fulminating type of purpura.

Platelet counts were done daily while the patients were in the hospital for treatment and at intervals of approximately 1 week to 1 or more months after discharge. The platelets were counted after the manner described by Rees and Ecker.[14] The fluid used for dilution was prepared according to the directions recommended by these authors and was filtered each time before use. A pipette calibrated for the enumeration of erythrocytes and certified for accuracy by the U. S. Bureau of Standards was used in the determination of the number of platelets per cubic millimeter of blood. After dilution the pipette was shaken for 5 minutes, the counting chamber loaded, but actual counting was not done until 10 minutes had elapsed to permit sedimentation of the platelets. The erythrocytes and leukocytes were counted in the usual manner. The hemoglobin determinations were made on the Sahli hemometer calibrated to read 14 gm. to 100 cc. of blood.

The determination of capillary resistance was estimated by the use of a sphygmomanometer with the cuff inflated to a pressure just below the systolic and sustained for 5 minutes. A definitely positive result was recorded if innumerable petechial hemorrhages appeared in the skin of the forearm.

During the period of Roentgen ray administration all other forms of therapy which might influence platelet production were omitted. In treating these patients the following factors were used: 200 kilovolts, constant potential; 15 milliamperes; target skin dis-

tance of 50 cm., composite filter consisting of 0.2 mm. of tin, plus 0.25 mm. of copper, plus 2 mm. of aluminum.

Using the above factors, the apparatus delivers 28.2 roentgens per minute, measured without backscatter. The size of the field used on the patient's skin varied with the size of the patient and the size of the spleen. The smallest was 10 by 10 and the largest, 10 by 20 cm. The rays were directed toward the spleen from the front, from the back and from the side. One field a day was used. The daily dose varied between 200 r. and 300 r., with a total of from 1200 to 3300 r. in 6 to 15 days.

Effect of Roentgen Ray on Platelet Production in Acute Recurring Thrombocytopenia. The 4 patients in this group showed a definite increase in their circulating blood platelets following Roentgen ray radiation over the spleen. It is to be noted in Figs. 1, 2 and 3 that the platelet response was prompt, and began within 24 to 48 hours after treatment was started. In 2 patients receiving a total of 1200 r. units (Figs. 1 and 3), the platelets rose from a level of less than 40,000 before treatment to that of 300,000 or more per c.mm. during the period in which the 10 days' treatment was continued. In another patient (Fig. 2), less intense treatment, namely, a total of 800 r. units, was given and a lapse of approximately twice this period of time occurred before the platelets attained a high peak. In Protocol 4 are the data on a female patient, aged 9 years, whose recurring purpura had been previously controlled by transfusions. After Roentgen ray therapy to the spleen, this young patient had a rise in blood platelets from a level of about 100,000 to 500,000 per c.mm. followed by a cessation of bleeding.

Coincident with the platelet response, it is to be noted in the protocols that there was a gradual lessening of the hemorrhagic tendency and a subsequent return to normal of the clotting mechanism. In addition, in 3 patients who had had increased fragility of the capillaries prior to treatment, the tourniquet test showed a negative response 10 days after treatment was first started.

It is of interest to note in Fig. 1 that a decrease in platelets occurred after treatment was stopped and progressed to a marked thrombocytopenia. A recurrence of purpuric symptoms occurred in this patient (Case 1) 7 months after the first attack of purpura. At this time a second course of Roentgen ray was given to the spleen and consisted of a total dosage of 1800 r. units administered over a period of 12 days. Again there was a prompt rise in platelets from a level of about 40,000 to over 300,000 per c.mm. within ten days.

A recurrence of thrombocytopenia and bleeding also occurred in the patient whose data are recorded in Fig. 3. A total second dosage of 3500 r. units was given to the spleen over a period of 12 days and was accompanied by a thrombocytosis and a disappearance of spontaneous bleeding. This patient had been taking

Sedormid just prior to both the first and second attacks, which may be of some etiologic significance.[15] A photograph of a stained film of the blood from this patient showing the absence of platelets is reproduced in Fig. 4 and another showing their reappearance after Roentgen ray radiation is reproduced in Fig. 5.

The subsequent course of the platelets in 2 of the patients is also shown in Figs. 1 and 2. In the first patient the platelets have remained above 300,000 per c.mm. for 3 months, and in the second patient, above this level for 7 months.

It is to be emphasized that a second favorable response in 2 patients following Roentgen ray radiation over the spleen lends considerable support to the idea that this form of therapy in adequate dosage does increase the number of circulating platelets.

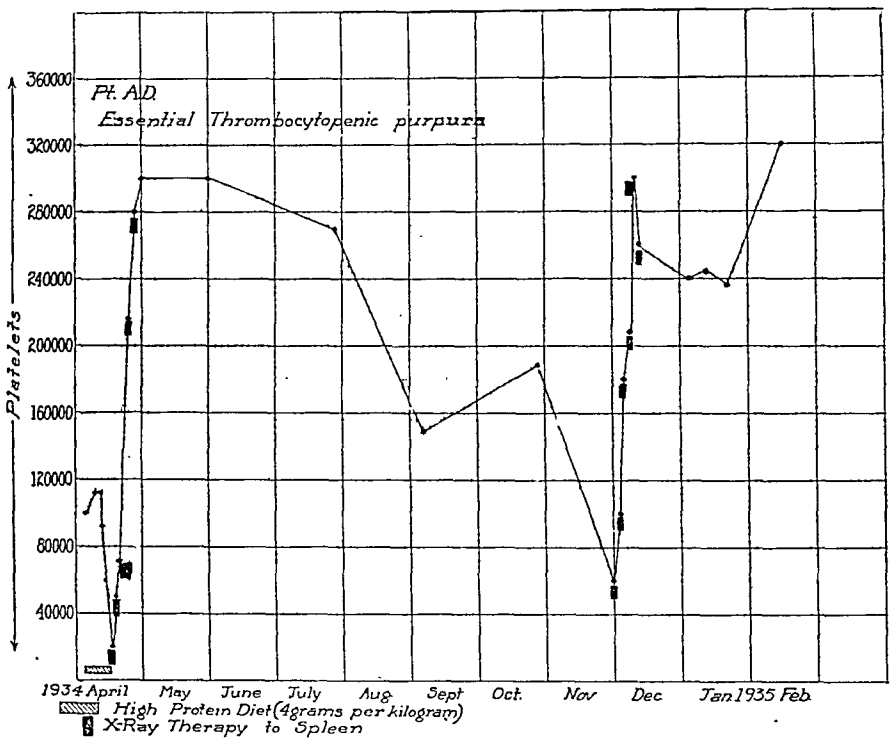


FIG. 1.—Effect of Roentgen ray radiation over the spleen on a patient (Case 1) with essential thrombocytopenic purpura hemorrhagica. Note the recurrence of thrombocytopenia and a second response to treatment.

Protocol. CASE 1.—A. D., a white American woman, aged 24, entered the University of California Hospital, April 3, 1934, stating that 2 months prior to hospital entry she had noticed the spontaneous occurrence of small hemorrhagic spots in the skin of the left breast. Since then, punctate purpuric spots had appeared at various places on her body. Associated with this was a marked tendency to bruise easily. Recently there had been slow oozing of blood from the gums and 4 brief periods of epistaxis. During this time her menses had been more profuse than usual. There was no history of the use of drugs, infections, or the association with chemi-

cals which might account for this hemorrhagic tendency. She had partaken of a well-balanced diet, including an abundance of vitamin C in fresh fruits and vegetables.

Physical Examination. On admission she appeared fairly well nourished and developed. There were small purpuric spots distributed over the body and there was a slight oozing of blood from the gums. There were no palpable lymph nodes in the cervical, axillary or inguinal regions, but there was slight splenic enlargement.

Laboratory Data. Examination of the blood showed: Erythrocytes, 4,160,000 per c.mm.; white blood cells, 5500 per c.mm.; and a hemoglobin concentration of 97% (13.6 gm., Sahli). The platelets were 112,000 per c.mm.; bleeding time, 25 minutes; clotting time within normal limits, but there was failure of the clot to retract. The tourniquet test was strongly positive for the appearance of petechial hemorrhages after 5 minutes' application.

Course of Illness. Within 9 days of hospital entry the platelets had dropped to 30,000 per c.mm., and by this time the patient had developed a slight hypochromic anemia. A high-protein diet was prescribed, calculated to yield 4 gm. of protein per kilogram of body weight. Bleeding became more profuse from the gums, epistaxis appeared, and large ecchymoses developed in the skin. Nine days after entry Roentgen ray treatment was started, and 6 exposures were given over a period of 12 days, at the end of which time bleeding had entirely subsided. The patient was discharged from the hospital, April 2, 1934, at which time the platelet count was 300,000 per c.mm.

On November 30, 1934, there was a slight recurrence of the hemorrhagic tendency, and at this time the platelets were 60,000 per c.mm. Over a period of 12 days 1800 r. units were administered and again the platelets rose to 300,000 per c.mm. The subsequent course of the platelets is recorded in Fig. 1.

CASE 2.—D. R., a white unmarried female, aged 23, was admitted to the University of California Hospital, September 19, 1934, complaining of epistaxis and bleeding gums of 4 months' duration. Three years prior to entry she had several episodes of epistaxis, prolonged bleeding when cut, menorrhagia, and bruised easily with slight trauma. After a few months this tendency to bleed lessened until the present illness. In the past she had had frequent coryza, occasional infection in the throat, and for many years had recurring acne scattered over her body. She had not used drugs nor had she knowingly been exposed to chemicals which might account for her condition. She had subsisted on an adequate diet.

Physical Examination. The patient was well developed and nourished. There was no apparent infection of the throat, but there were some small acneform pustules in the skin of the face and back. No enlarged superficial lymph nodes could be felt. The tip of the spleen was felt 2 cm. below the left costal margin. There were some bloody incrustations in the right nostril and some recent and fading ecchymoses in the skin of the lower extremities. The application of the sphygmomanometer with the cuff inflated to a pressure just below the systolic showed the presence of large numbers of petechiæ in the forearm at the end of 5 minutes.

Laboratory Data. Examination of the blood showed: Erythrocytes, 4,310,000 per c.mm.; hemoglobin, 66 % (9.2 gm., Sahli); leukocytes, 9000 per c.mm. The bleeding time was slightly prolonged and retraction of the clot did not occur until the end of 12 hours.

Course of Illness. Between September 24 and October 3 the patient received 4 Roentgen ray treatments over the spleen, with a total dosage of 800 r. units. Twenty days after treatment was started the platelets were 210,000 per c.mm., the bleeding time 3 minutes and the clot retraction

normal. Six months after treatment the platelets were 420,000 per c.mm. The course of the platelets in this patient are recorded in Fig. 2.

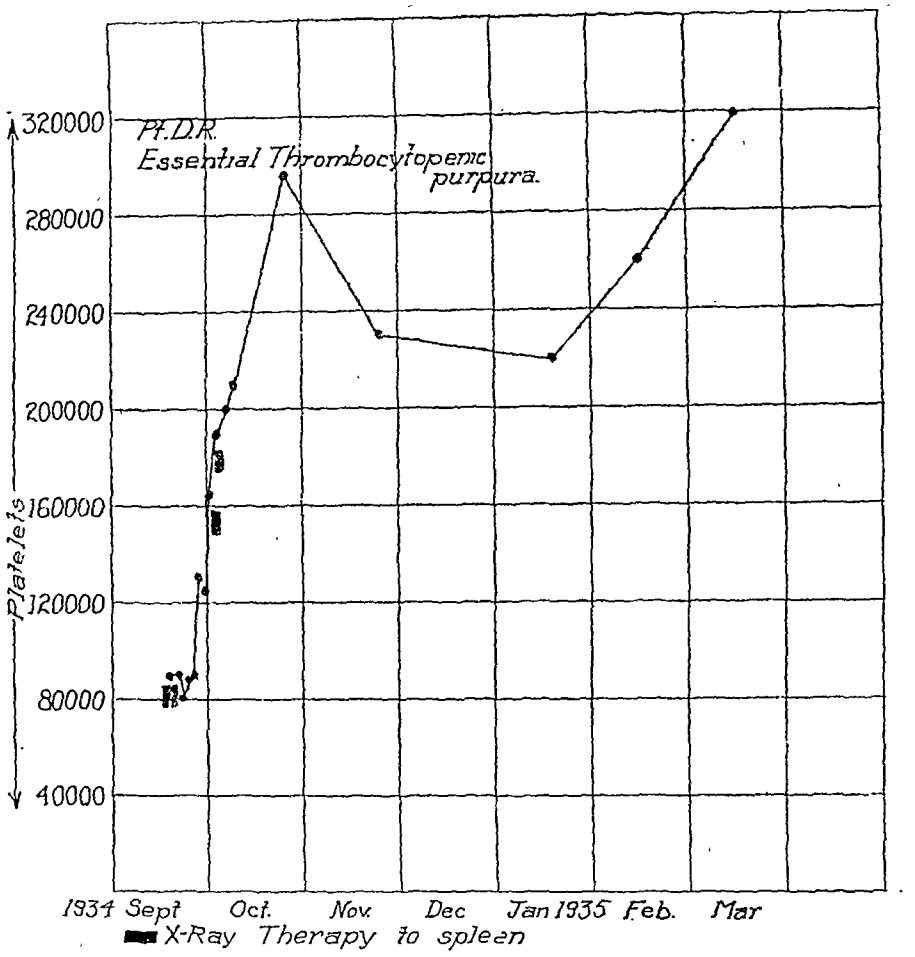


FIG. 2.—A slightly delayed reaction in a patient (Case 2) receiving less intense radiation.

CASE 3.*—M. C., an Italian female, aged 67, had been under the care of her physician for essential hypertension, arteriosclerosis and diabetes mellitus. Medication had consisted of insulin, digitalis folia and Sedormid tablets for pain. Her first entry into the hospital was November 18, 1934, at which time she complained of hemorrhagic spots on her legs and bleeding from the gums of 2 days' duration. The day prior to entry she had noticed blood in the urine. She had never noticed a hemorrhagic tendency until the present illness.

Physical Examination. The patient was moderately obese. There was no apparent ulceration of the pharyngeal structures. No large lymph nodes could be felt. The spleen was not palpable on deep inspiration. There were scattered purpuric spots and ecchymoses over the entire body but particularly on the arms and legs. There were petechial hemorrhages on the conjunctivæ and a small amount of blood was oozing from the nasal passages and from the gums. The tourniquet test was strongly positive for capillary hemorrhages.

* We express our thanks to Dr. John Sampson for permission to study this patient.

Laboratory Data. Examination of the blood showed: Erythrocytes, 4,470,000 per c.mm.; leukocytes, 10,800 per c.mm.; platelets, 40,000. The clotting time was 25 minutes and the clot failed to retract.

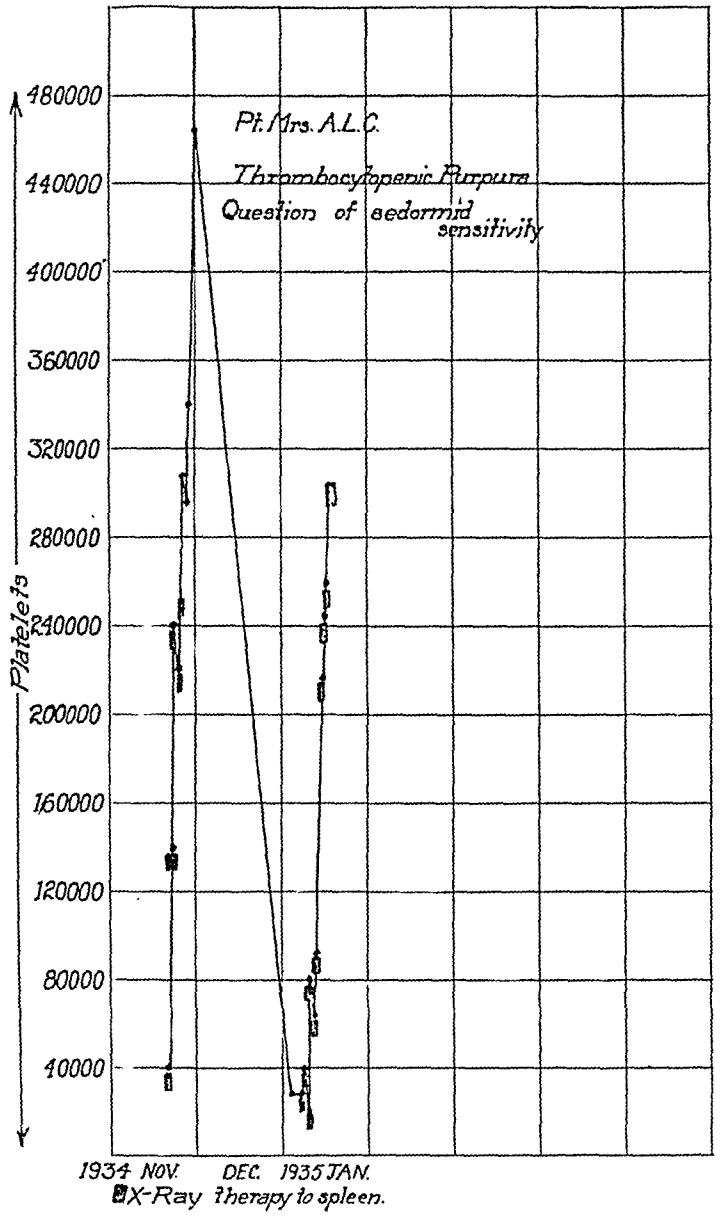


FIG. 3.—Effect of Roentgen ray radiation of the spleen on a patient (Case 3) with recurring thrombocytopenia believed due to Sedormid sensitivity.

Course of Illness. Roentgen ray therapy over the spleen was started on the day of entry, and after 6 exposures, 1 given on each successive day, the platelets had risen to 300,000. Application of the sphygmomanometer failed to show the presence of petechial hemorrhages. The bleeding tendency disappeared and the patient was discharged from the hospital,



FIG. 4.—A typical field from a blood smear of Case 3 before Roentgen ray treatment. Note the absence of platelets.

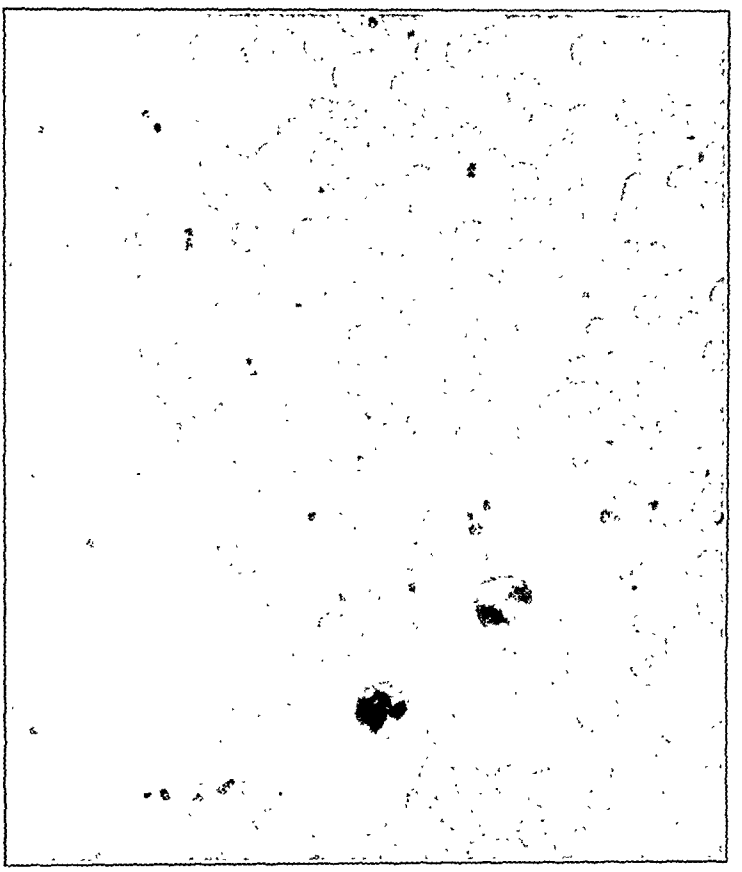


FIG. 5.—A typical field of a blood smear from Case 3 after Roentgen ray radiation. Note the presence of large numbers of platelets.

November 30, at which time the platelets were 468,000 per c.mm. Bleeding time was 1½ minutes and there was normal retraction of the clot. The patient was seen on January 4, 1935, when again she showed marked bleeding from mucous membranes and into the skin. The platelets were 30,000 per c.mm. The bleeding time was longer than 25 minutes and there was failure of the clot to retract. It was learned that she had started taking Sedormid tablets just prior to the onset of this second episode of bleeding. Roentgen ray therapy was started on January 7, and the patient was given treatment over the spleen daily for a total of 11 exposures, or 3300 r. units. On January 8, the platelets were 300,000; the bleeding time, 3½ minutes, with a normal retraction of the clot. Data showing Roentgen ray therapy and the course of the platelets in this patient are shown in Fig. 3.

CASE 4.—V. D. S., a schoolgirl, aged 9, entered the San Francisco Hospital, May 5, 1935, because of bleeding from the mouth and hemorrhages in the skin of the abdomen and legs. She had had 2 previous hospital admissions at about 10 months' intervals. On these occasions her symptoms were similar and her blood platelets were about 85,000 per c.mm. A diagnosis of thrombocytopenic purpura was made. Treatment consisted of the intravenous administration of whole blood followed by a subsidence of her symptoms. The child had been fairly well until the present entry, except that she had noticed slight bleeding from the gums on occasions. On the day of entry she developed profuse bleeding from the gums and several hemorrhages appeared over her body. There was no history of medication or exposure to chemicals which might account for the bleeding. She had eaten on the average of 1 orange a week.

Physical Examination. The patient was well nourished and developed, active, coöperative, intelligent and resting quietly in bed. There were no demonstrable enlargements of the lymph glands and the spleen was not palpable. There was no evidence of infection. Blood was oozing slowly and continuously from the gums, and there were many petechial and ecchymotic hemorrhages scattered over the body.

Laboratory Data. The red blood cells were 4,200,000 per c.mm., and the leukocytes 8600 per c.mm., with a normal differential count. The hemoglobin was 80% (Sahli). A specimen of venous blood clotted in 7 minutes, but there was a failure of the clot to retract. Following a puncture of the ear, bleeding continued for 32 minutes. The platelets were about 100,000 per c.mm.

Course of Illness. The patient received Roentgen ray treatment over the spleen consisting of 200 r. units daily, alternating anteriorly and posteriorly for 8 days, making a total of 1600 r. units. Seven days after treatment was started, the laboratory data showed the bleeding time to be reduced to 8 minutes and the platelets increased to 500,000 per c.mm. One week later the laboratory data were essentially the same.

Effect of Roentgen Ray Therapy on Patients With Chronic Thrombocytopenia With Recurring Purpura. The course of illness in 2 of our patients was characterized by recurring purpura and various forms of treatment for the control of bleeding had been tried off and on over a period of 1 or more years. Such therapeutic agents were given as daily injections of liver extract (343 NNR), large doses of iron by mouth (iron and ammonium citrate, U. S. P., 6 gm. daily), calcium by mouth and a diet high in calcium, spleen marrow, lextron, pentnucleotide and multiple transfusions. The best results, so far as cessation of bleeding was concerned, were obtained from

repeated transfusions, but with any of the methods there was little or no actual increase in the total number of platelets.

In Fig. 6 are shown a summary of the treatment and the graphic presentation of the platelets of a patient (Case 5) who was observed over a period of 22 months. The platelets during this time varied between 40,000 and 80,000 per c.mm., going as high as 120,000 on one occasion after 3 transfusions of whole blood. It is to be noted in the figure that following Roentgen ray treatment over the spleen this patient's platelets rose to a peak of 270,000 per c.mm. Coincident with this, the loss of blood from the gums stopped and the petechial hemorrhages which had accompanied the thrombocytopenia gradually faded. In addition, a specimen of blood coagulated within normal time and soon after developed a firm retractile clot. It is of interest to note, however, that the platelets did not remain at a high level, but 6 weeks after treatment was first started had returned to a low figure of 120,000 per c.mm.

The diagnosis of the disease from which this patient (Case 5) and the following one (Case 6) suffered is not clear-cut, but the data suggest that of chronic thrombocytopenic purpura with anemia, rather than chronic aplastic anemia, aleukemic leukemia, or depressed marrow function as a result of infection or neoplasm.

In Fig. 7 is recorded the course of the platelets in a patient (Case 6), aged 4 years, who had had recurring attacks of thrombocytopenia and purpura while under observation for a year. During this time small transfusions of whole blood given at frequent intervals on 3 different occasions and finally splenectomy caused a rise in platelets from about 40,000 to as high as 80,000 per c.mm. It was at first thought that the patient had an accessory spleen which might account for the recurrence of symptoms after splenectomy, and, with this in mind, it was decided to give him Roentgen ray radiation over the abdomen. This was not done, however, and in its stead treatment was directed over the long bones. In Fig. 7 it is to be noted that a sharp rise in platelets from a low level of 60,000 per c.mm. occurred soon after treatment was started and within 9 days reached a peak of 270,000. As in the previous case, however, the platelets began to decrease after treatment was stopped.

Protocol. CASE 5.—J. S., a married male, aged 60, was first seen, February 3, 1935, and has been under observation since that time. He has had recurring attacks of epistaxis, bleeding from the gums, petechial hemorrhages in the skin, and had noticed that he bruised easily with slight trauma. He has also had symptoms of dyspnea and palpitation following exertion.

Physical Examination. A moderately obese, well-developed, pale man of stated age. There were no enlarged lymph glands and the spleen was not enlarged. There was no evidence of heart disease. During the past 2 years, the number of red blood cells varied between 750,000 and 3,000,000 per c.mm., and the percentage of hemoglobin varied between 10 and 75%

(Sahli). The number of leukocytes varied between 2000 and 6000 per c.mm. Repeated differential counts revealed normal percentages, with the exception of the presence of from 1 to 5% myelocytes and from 10 to 20% of non-filament cells. Rarely was a cell similar to a myeloblast observed. The percentage of the reticulocytes was always slightly increased, the highest figure being 6 and the lowest 2. The blood platelets were reduced and varied in numbers from 40,000 to 100,000 per c.mm. The bleeding time was over 25 minutes and many petechial hemorrhages appeared after the tourniquet test. Coagulation time was $4\frac{1}{2}$ minutes, but the clot was friable and did not retract.

Course of Illness. The Roentgen ray therapy, consisting of a total of 1200 r. units, and the course of the platelets in this patient are recorded in Fig. 6.

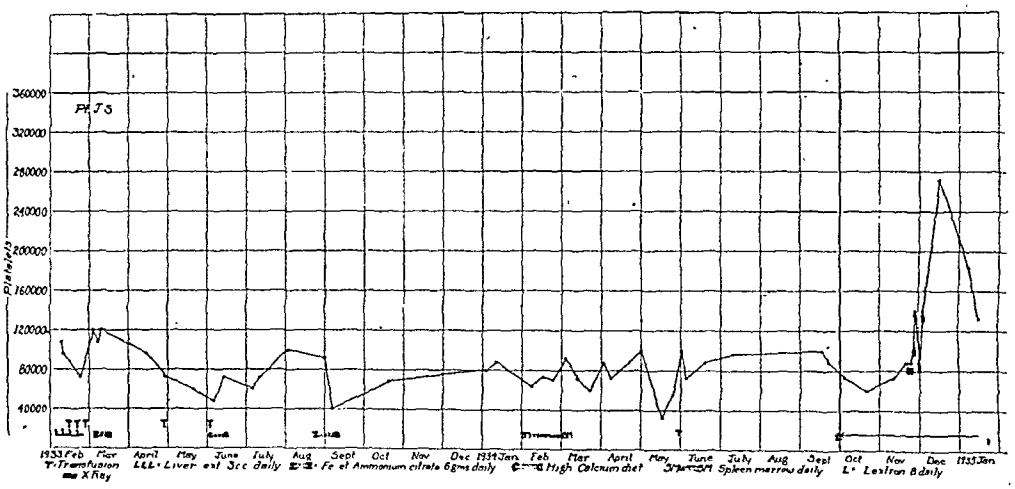


FIG. 6.—Showing the negative effect of various therapeutic measures on platelet production in a patient (Case 5) with chronic thrombocytopenia but a definite increase after Roentgen ray radiation.

CASE 6.*—R. S., a boy, aged 6, was first seen, January 9, 1934, complaining of slight epistaxis and bruising of the skin of 2 years' duration.

Physical Examination. The patient was undernourished and there were fading ecchymoses in the skin. The spleen was slightly enlarged.

Laboratory Data. Examination of the blood at frequent intervals during the past year showed a variation in the number of red blood cells between a level of 1,000,000 to 3,000,000. The white blood cells fluctuated between 1200 and 8000. Repeated differential counts revealed normal percentages of the various white blood cells. Prior to Roentgen ray therapy, the platelets were markedly reduced and varied in numbers between 30,000 and 100,000 per c.mm. The capillary clotting time was 10 minutes. The clot did not retract.

Course of Illness. Various therapeutic agents and multiple transfusions were tried on this patient without definite effect on the platelet count. Cessation of the hemorrhagic tendency did occur for short periods of time after transfusion. Finally, the patient was given transfusions in the amount of 200 cc. of whole blood daily for 6 days, followed by the removal of the spleen. The platelets at this time were 80,000 per c.mm., and

* The authors wish to thank Dr. F. S. Smyth, of the Division of Pediatrics for permission to study this patient.

within 2 months had dropped to less than 60,000 per c.mm. It was considered advisable at this time to give the patient Roentgen ray treatment over the long bones. Data relative to treatment and the platelets in this patient are reported in Fig. 7.

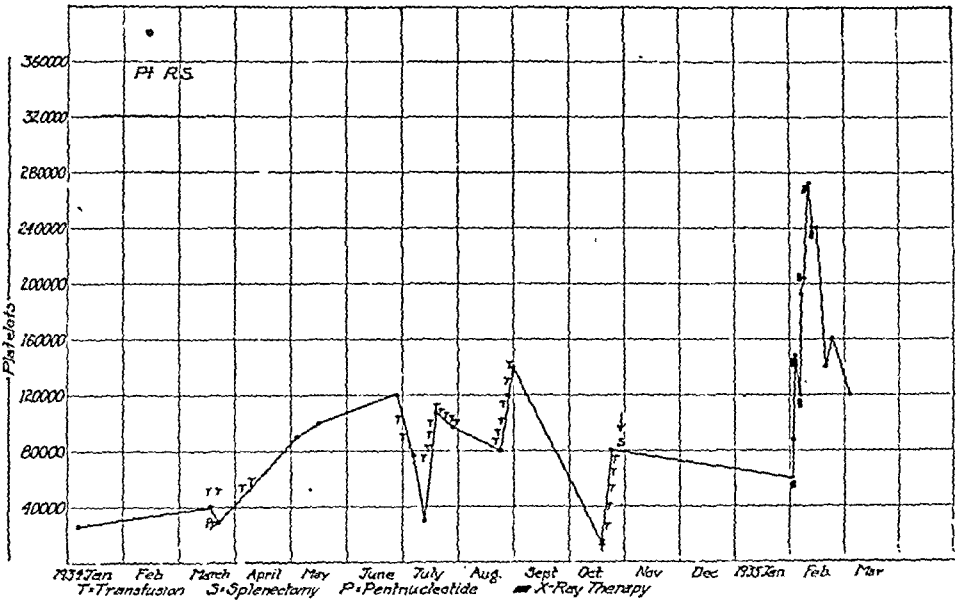


FIG. 7.—Showing a moderate increase in platelets in a patient (Case 6) following multiple transfusions; no effect after splenectomy but a marked rise after Roentgen ray of the long bones.

TABLE 1.—SHOWING LABORATORY DATA AND COURSE OF ILLNESS ON CASE 7.

Name: Mr. R. H. Age: 40 Sex: ♂

Diagnosis: Idiopathic Purpura Hæmmorhagica (Fulminating Type)

Date.	R.B.C.	Hgb. % Gm.	Platelets.	W.B.C.	X-Ray.	Notes.
1–5–35	4.81	94–13.1	40,000	12,800	×	Bleeding time 14½ minutes +. Coagulation time 8 minutes.
1–7–35	2.35	54–7.6	20,000	21,800	×	5 P.M. — 200 cc. transfusion.
4 P.M.	2.23	43–6.0	30,000			
1–8–35 9 A.M.	2.04	32–4.5	None seen in counting chamber.	20,100	×	Splenectomy— 1:30 P.M.
2.00 P.M.	1.45	35–5.0	30,000	70,400	..	Count made 5 minutes after splenic vessels clamped.
4.10 P.M.	1.38	32–4.5	78,000		..	Patient died 12 o'clock midnight

The Ineffectiveness of Therapy in Acute Fulminating Purpura. In Table 1 are presented the data on a middle-aged man (Case 7), who entered the hospital with an acute type of idiopathic purpura hæmorrhagica progressing to a fatal termination. It is to be

noted that at the time of entry this patient's red blood cells and hemoglobin were within normal limits, but there was a marked reduction in the number of platelets. Roentgen ray therapy was given to this patient in the same way it was given to the others. Despite this régime, however, there was a progression of the hemorrhagic tendency and the rapid development of a severe anemia. Finally, splenectomy was performed and was followed 12 hours later by the death of the patient from hemorrhage.

Protocol. CASE 7.—R. H., a man, aged 40, entered the University of California Hospital, January 4, 1935, complaining of bleeding from the nose and gums and of bloody urine. The day prior to entry the patient awakened in the morning and found his mouth full of blood. He went to a physician who told him that he was bleeding from the nose and gums. During the night he noticed, for the first time, bloody urine. His occupation was that of a salesman, and he knew of no exposure to benzol, arsenic, lead or other heavy metal or Roentgen ray. The only drug consumed was aspirin, in daily amounts of 10 to 20 grains, at varying intervals during the past 3 weeks. Three weeks prior to the present illness he had had an upper respiratory infection, but there were no symptoms referable to this condition during the past week. There was no past history of bruising easily or of prolonged bleeding.

Physical Examination. The patient was well developed and nourished, quite apprehensive and showed continuous bleeding from the nose and gums, and there were large hemorrhagic blebs beneath the mucous membrane of the mouth. Scattered over the entire body were petechial hemorrhages and small ecchymoses. No enlarged glands could be felt and the spleen was not enlarged to palpation. The tourniquet test was markedly positive for petechial hemorrhages.

The laboratory data and the course of the disease for this patient are shown in Table 1. It is to be noted that in spite of Roentgen ray therapy, transfusion and splenectomy, the disease was progressive and the patient died 5 days after the onset of illness.

Discussion. From our observations presented here, it appears that by Roentgen ray radiation in adequate dosage over the spleen or long bones, an increase in blood platelets will occur in patients with essential thrombocytopenic purpura hæmorrhagica. Accompanying this there is a cessation of bleeding and a disappearance of the hemorrhagic tendency.

It is difficult to explain this phenomenon adequately. The rise in platelets begins soon after 1 or 2 treatments and, accordingly, before a sufficient number of radiations have been given to cause marked destruction of splenic tissue. Apparently, the reaction is not one of so-called "Roentgen ray splenectomy," and, therefore, the response is not similar to the thrombocytosis that follows surgical removal of the spleen.

One of the theories concerning causation of thrombocytopenia is that of phagocytosis of platelets by cells of the reticulo-endothelial system. In view of this idea, it may be suggested that Roentgen ray radiation either prevents the continuation of this process or causes a release of platelets already engulfed.

There is now considerable evidence[16, 17] at hand to support Wright's theory that the megakaryocytes of the bone marrow are chiefly concerned in the production and release of the blood platelets. We have insufficient data to prove that platelet production following radiation is a result of increased activity of the megakaryocytes. Since treatment was directed over the spleen in all of our patients with but one exception, there is very little to suggest any direct effect of this form of therapy upon the megakaryocytes. Further work is indicated wherein studies on bone marrow removed by biopsy from patients under treatment may be correlated with platelet production.

It is quite evident from our results that Roentgen ray therapy is not entirely satisfactory so far as curative results are concerned. In some of our patients a recurrence of symptoms appeared from 1 to 7 months after treatment was stopped. It is to be emphasized, however, that a rise in blood platelets did occur in 6 out of 7 of our patients.

Summary and Conclusions. Seven patients with essential thrombocytopenic purpura comprised a series for study on the effect of Roentgen ray therapy in platelet production. Prior to treatment the platelets were about 10,000 per c.mm. in 1 patient and varied between this figure and 40,000 in the others. Six patients received Roentgen ray therapy over the spleen and 1 over the long bones in doses of 200 r. units. Two patients had a recurrence of symptoms and were given 300 r. units during a second course of treatment. The patients received a total of from 1200 to 3300 r. units. Six of these patients showed an increase in platelets, beginning within 24 to 48 hours, going up to as high as 250,000 to 500,000 per c.mm. in 9 days. In 1 patient with chronic thrombocytopenia of 2 years' duration, no effect was shown following liver extract therapy, multiple transfusions, large doses of iron and ammonium citrate daily, high-calcium diet, spleen marrow or lextron, but a definite rise in platelets occurred following Roentgen ray treatment. In 1 patient a high-protein diet failed to increase the platelets, but there was a rise after Roentgen ray treatment. In another patient there was a recurrence of symptoms following splenectomy and an increase in platelets was stimulated by Roentgen-ray therapy over the long bones. In still another patient no increase of platelets was produced by Roentgen ray or splenectomy and the patient died as the result of hemorrhage.

It is concluded from these studies that Roentgen ray radiation of the spleen in doses of from 200 to 300 r. units will cause an increase in blood platelets in patients with idiopathic thrombocytopenic purpura hæmorrhagica.

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POSTOPERATIVE RESPIRATORY COMPLICATIONS: OCCURRENCE FOLLOWING 7874 ANESTHESIAS.

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Pulmonary complications following anesthesia with certain of the agents, have been thought to greatly exceed such complications after the use of other agents. Writers have pointed out an advantage with nitrous oxid, spinal and other anesthetic drugs since they are

not irritant to the respiratory tract and do not increase secretions. Too often such reports have not been substantiated by accurate, carefully collected statistics. They may merely represent the author's impression or may consider one single factor, namely the agent. It has been a firm conviction in this clinic that other factors such as the ability of the surgeon and anesthetist, the anesthetic technique, the time required for operation, the depth of narcosis and many other circumstances should be taken into account in evaluating postoperative morbidity and mortality. It was to correlate the majority of the factors common to surgical procedures and learn their influence on postoperative pulmonary complications that the present study was undertaken.

It is readily agreed that statistics are not infallible but if they are carefully recorded and tabulated they offer a worthy substitute for vague conclusions which cannot be verified by records. The statistics in this report were compiled from the records completed during the calendar years 1933–1934. They represent the first 2 year's experience with an improved anesthetic record system at the Wisconsin General Hospital.[1]

All anesthetics included in this report were administered by members of the Department of Anesthesia. Minor operations completed with local infiltration anesthesia by the surgeon are not considered. Senior medical students who spend 1 week on the service, interns for the month of their rotating service spent in anesthesia, residents of 1 or 2 years' experience, the assistants and the chief of the service comprise this department. The surgery was performed by the same staff under similar conditions in a single hospital. The anesthetic agents included were those in common use: ether, nitrous oxid (N_2O), ethylene (C_2H_4), tribromethanol (T. B. E.), procain, together with cyclopropane (C_3H_6) an experimental drug unfamiliar to the staff before 1933. Chloroform, barbituric acid derivatives and other drugs used in less than 100 cases were not included.

The statistics were carefully collected by the anesthetic department after a definite scheme. The patient was visited before operation and the clinical record examined. The patient was seen postoperatively on the third to fifth day. If complications were present, later visits were made. Finally the case was reviewed to complete the record at time of discharge or death. Such data were transferred to a punch card and tabulated by machine.[1]

Premedication varied little. Morphin and scopolamin were given to most of the cases. A barbituric acid derivative was given to patients when procain anesthesia was anticipated. Atropin was used occasionally. Obstetrical cases, infants, and some others usually had no premedication.

Table 1 lists the complications considered in this report. The number of times each complication was noted and the percentage

incidence are listed. No effort has been made to differentiate complications as due to surgery, anesthesia or the preëxisting condition of the patient. A very liberal interpretation of complications was made. None were omitted. Respiratory complications present before operation were not listed as postoperative complications in those cases where surgery was undertaken as a treatment for the condition. For example, a patient with pulmonary tuberculosis treated by thoracoplasty was not considered as having tuberculosis as a postoperative complication. However, a patient coming to surgery with pharyngitis or cough was recorded as having pharyngitis or cough postoperatively if the condition was aggravated by surgery or in any way complicated convalescence. The item "sore throat" in Table 1 was used to designate resulting trauma in cases anesthetized by endotracheal technique. The same complication following the use of any other technique was listed as laryngitis.

TABLE 1.—RESPIRATORY COMPLICATIONS IN 7874 ANESTHESIAS.

Complications.	No.	Percentage of all cases.
Pneumonia, lobar and bronchial	49	0.60
Pneumonia, hypostatic	8	0.10
Pneumonia, tuberculosis	2	0.02
Collapse, partial	22	0.30
Collapse, massive	13	0.20
Bronchitis	22	0.30
Laryngitis	144	1.80
Cough, slight	287	3.60
Cough, severe	89	1.10
Hiccough	35	0.40
Obstruction, upper respiratory	32	0.40
Rhinitis	27	0.30
Pleurisy	11	0.10
Sore throat*	33	0.40
Miscellaneous	24	0.30
All respiratory complications	..	6.00

* Endotracheal anesthesia only.

The time of occurrence of the complications shown in Table 1 varied greatly. The postoperative period was not limited to any definite number of days. A pneumonia developing on the fourteenth day following inguinal herniorrhaphy would be included, while the same complication occurring as a terminal event months after a celiotomy in an inoperable carcinoma case would be excluded and the cause of death given as carcinoma. An effort was made to include every major and minor respiratory complication that might possibly be related to the surgical procedures regardless of when it occurred.

Figure 1 graphically represents the percentage incidence of respiratory complications for each month of the year. During the first year of the study an attempt was made to correlate respiratory complications with average temperatures and humidities. Postoperative complications could not be anticipated from existing

weather conditions. Certain factors such as a severe dust storm during July, 1934, may explain an increase of respiratory complications that month.

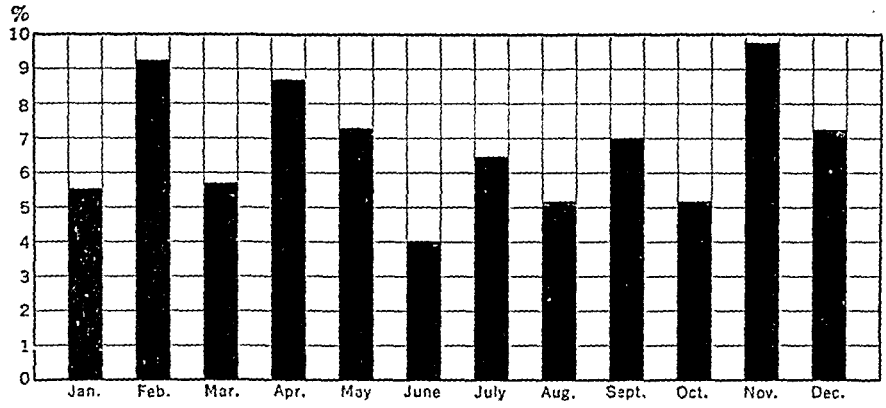


FIG. 1.—Percentage incidence of respiratory complications for each month.

It was definitely established for the year 1933 that the incidence of postoperative respiratory complications was greater during the same months that respiratory diseases had an increased prevalence among university students as shown by student health records.

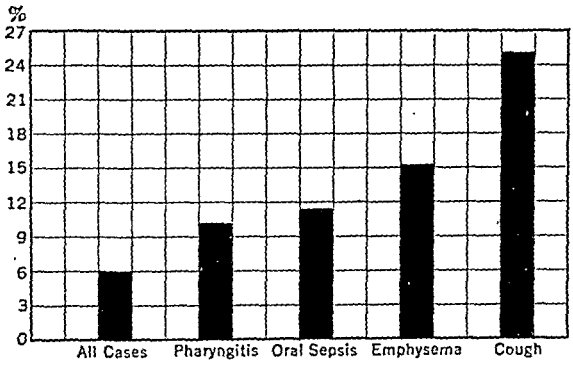


FIG. 2.—The percentage incidence of postoperative respiratory complications in patients with certain pre-operative conditions diagnosed.

The significance of the preoperative respiratory conditions of patients operated upon is evident in Fig. 2. In this series 6% of all cases anesthetized developed some minor or major respiratory complication following operation. Those patients having pharyngitis, acute or chronic, before operation, showed a total incidence of more than 10% of postoperative respiratory complications. If oral sepsis was present, the incidence was nearly double that of all cases, while in cases having a cough, over 25% had the postoperative convalescence complicated by some respiratory abnormality.

A comparison of the complications following the use of various agents is shown in Fig. 3, and the different complications for these agents are listed in Table 2. That fewer complications would follow

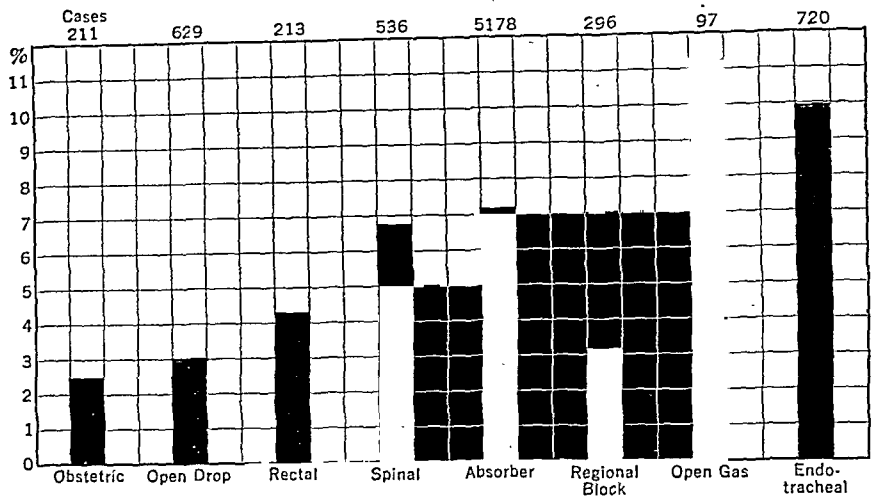


FIG. 3.—The number of anesthesias with each agent and the comparison of the post-operative respiratory complications represented graphically in percentages.

the use of nitrous oxid was expected since that agent was used in obstetrical analgesia, in dental extractions and in many superficial operations. Tribromethanol was used almost exclusively in good risk patients for ocular surgery, and was given only 213 times.

TABLE 2.—COMPLICATIONS WITH EACH AGENT.

	N_2O, %.	C_2H_4, %.	Ether, %.	C_3H_6, %.	Proc., %.	T.B.E., %.
None	94.50	86.10	92.20	93.50	92.00	94.30
Pneumonia, lobar and bronchial	0.31	0.30	0.24	0.41	0.72	0.47
Pneumonia, hypostatic	0.10	0	0.30	0.03	0.38	0
Collapse, partial	0.21	0.61	0.43	0.16	0.12	0
Collapse, massive	0	0.10	0.30	0.12	0	0
Bronchitis	0.10	0.38	0.51	0.28	0	0
Laryngitis	2.40	2.00	1.80	1.90	0.84	1.80
Cough	2.40	6.40	6.20	3.60	5.16	2.30
Hiccough	0.10	0.38	0.80	0.28	1.07	0
Obstruction, upper respiratory	0.31	0.71	0.90	0.22	0.12	0
Rhinitis	0.41	0.61	0.51	0.19	0.48	0.47
Pleurisy	0.21	0	0.30	0.12	0.38	0

A comparison of the seriousness of the risks done with each agent is shown in Table 3. Anesthetic risks were classified as follows: "Emergency" patients who, previous to operation, had insufficient clinical examinations to permit a feasible estimation of the risk. "A"—Patients in excellent physical condition to undergo a minor operation. "B"—Patients in good physical condition who are to

undergo a serious operation, or those whose physical condition is impaired but a minor procedure contemplated. "C"—Patients who have a definite organic lesion or lesions other than that for which a serious operation is to be undertaken but which should not be expected to be fatal in the near future. "D"—Patients with a very serious physical handicap which might prove fatal in the not distant future, and are to have an operative procedure of an extremely serious nature. "DD".—Patients whose condition is desperate, where the possibility of death at operation is not remote, and without operation is likely. Table 3 shows that the larger per cent of the serious risks were done with cyclopropane, ethylene and ether in the order named.

TABLE 3.—ANESTHETIC RISKS WITH EACH AGENT.

Agent.	Emergency.	A.	B.	C.	D.	DD.
N_2O	32.7	11.7	35.9	16.0	3.2	0.41
C_2H_4	16.8	6.9	39.4	28.9	6.9	1.02
Ether	17 2	10.7	39.7	25.5	6.0	0.83
C_3H_6	16.4	4.5	33.2	35.6	8.7	1.50
Procain	5.7	5.2	41.1	44.5	2.9	0.48
Tribromethanol	16.2	5.6	50 2	21.1	6.8	0
Total	17.5	8.4	36.8	29.6	7.2	0.49

Figure 4 compares the complications for the various risks. Two-thirds of the patients were in the "B" and "C" classification. Very few were in the "DD" group (Table 3).

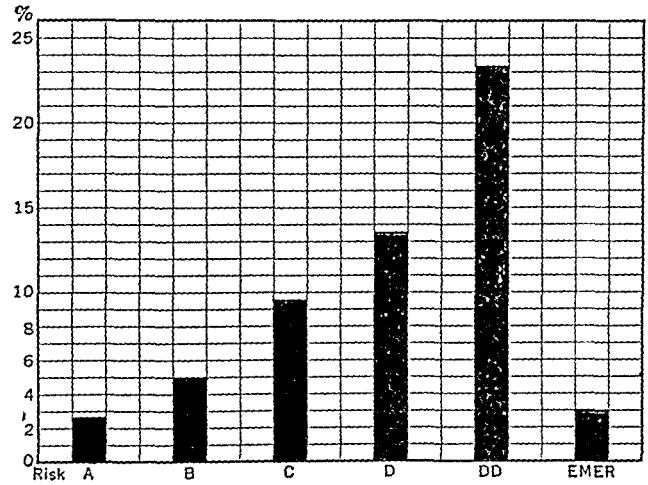


FIG. 4.—Postoperative respiratory complications found in different surgical risks.

The anesthetic agents employed for the different surgical procedures are shown in Table 4. General surgery, including thyroid

and central nervous system operations, was more often accomplished with cyclopropane, ether and ethylene. A large per cent of nose and throat operations were done with ether, since tonsillectomies for children are included. In each case, the agent producing the more profound degree of narcosis is credited as the anesthetic for that operation. A nitrous oxid-ether sequence was considered an ether anesthesia. Likewise if ether was used to facilitate tracheal intubation and the anesthesia maintained with ethylene or nitrous oxid, the case was recorded as an ether anesthesia. If tribromethanol was used and supplemented by a gaseous agent, the former received credit for the case.

TABLE 4.—AGENTS USED FOR DIFFERENT SERVICES.

Operation.	Agents.								
	N_2O.	C_2H_4.	Ether.	$CHCl_3$.	C_3H_6.	Proc.	T.B.E.	Others.	Total.
General surgery	241	370	456	9	1190	413	9	16	2704
Orthopedic	134	279	289	1	729	44	0	2	1478
Gynecologic	272	188	210	0	744	8	5	76	1503
Obstetric	211	33	10	0	62	1	0	0	317
Genito-urinary	23	43	42	0	214	341	6	0	669
Ear, nose and throat	10	16	407	3	66	0	1	2	505
Eye	16	2	13	0	33	0	185	2	251
Plastic	7	18	166	1	75	1	4	0	272
Dental	39	22	98	0	66	1	0	40	266
Others	0	0	1	0	9	1	0	0	11
Anesthesia only	4	3	14	0	15	9	3	1	49

Figure 5 compares the percentage incidence of respiratory complications following the use of various anesthetic techniques. It might be expected that few complications would follow the inter-

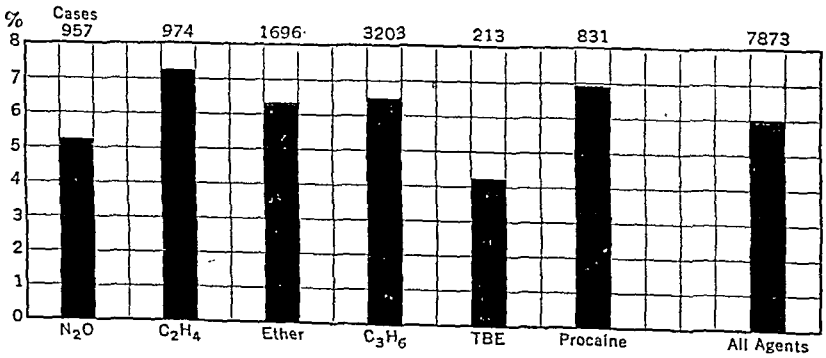


FIG. 5.—The percentage incidence of postoperative respiratory complications following the different anesthetic methods employed. The number of cases anesthetized by each technique is shown.

mittent use of gas in obstetrical cases and this was found to be true. The open drop ether anesthesias were, in more than 60% of the

cases, done for tonsillectomies in children. The technique was not used for abdominal surgery and never selected when a serious risk was undertaken. The rectal technique was used for tribromethanol anesthesia, and in more than 90% of the cases, for ocular surgery. Spinal technique was more often chosen for genito-urinary surgery. Some lower and upper abdominal cases were anesthetized by intradural injections, but the technique was avoided in celiotomies if the patient was considered more than a "C" risk. Patients anesthetized by regional block presented, in a large per cent of the cases, serious circulatory or other complications, as for example, transurethral prostatic resections in aged men with advanced circulatory path-

TABLE 5.—CASES ANESTHETIZED BY THE ENDOTRACHEAL TECHNIQUE.

Surgery.	Total cases.	Risks.					
		E.	A.	B.	C.	D.	DD.
Dental	160	34	15	75	35	1	0
Ear, nose and throat	25	6	1	7	11	0	0
Plastic	86	15	1	49	20	1	0
Eye	12	2	0	7	3	0	0
Kidney	6	0	0	2	3	0	1
Gynecologic laparotomy	26	1	1	13	12	0	0
Craniotomy	63	2	0	0	18	41	3
Thyroid	12	2	0	2	5	2	1
Thoracic	8	0	0	0	1	7	0
Gall bladder	57	5	0	5	43	4	0
Gastro-intestinal	112	4	1	13	46	46	0
Hernia	15	1	0	5	9	0	0
Rectal	12	0	0	1	4	7	0
Laminectomy	29	2	1	1	16	5	4
Bone and joint	26	5	1	8	11	1	0
Others	73	7	2	23	30	9	2
Total cases	722	86	23	211	267	124	11
Per cent of total cases	..	11.9	3.2	29.2	36.9	17.1	1.5

ology. The remainder were minor operative procedures and rectal operations. Open gas technique (mask with exhalation valve and partial rebreathing) was not often used. It was never selected for serious operations. The incidence of complications may be unfair to this technique since the series is so small. Carbon dioxid absorption technique[2] was used for the majority of administrations. When endotracheal intubation is to be done, the tracheal airway merely replaces the face mask in the absorption technique. Endotracheal intubation is rarely used for other than serious risks except in intraoral surgery and exodontia. Surgery of the central nervous system, gastro-intestinal tract and gall bladder comprise the major-

ity of the cases. That the more serious and complicated surgical procedures are accomplished with endotracheal anesthesia is evident in Table 5 which lists the surgery, number of cases, and risk for that technique.

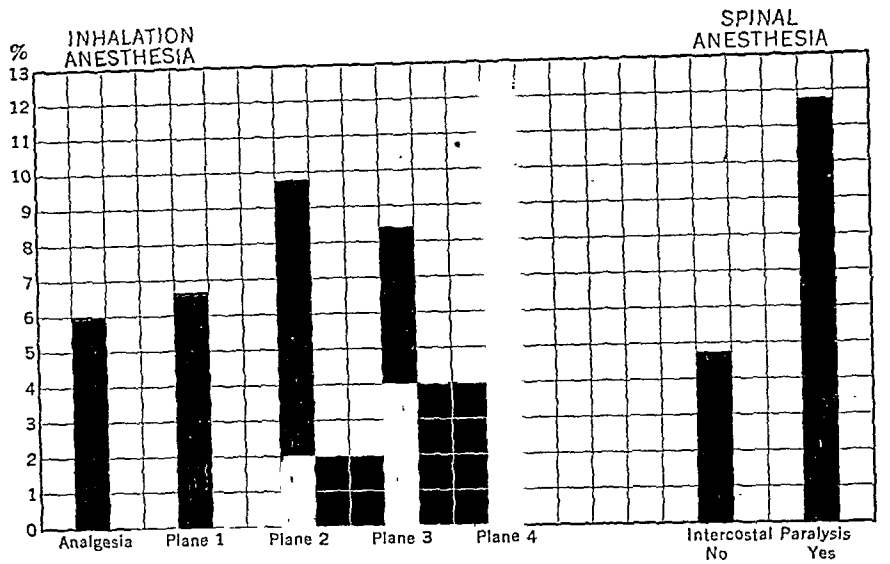


FIG. 6.—Percentage incidence of postoperative respiratory complications for the different planes of anesthesia. In spinal anesthesia the cases with paralysis of the intercostal muscles are compared with those where no such paralysis occurred. Regional anesthesias other than spinal block are omitted.

That the degree of narcosis is a factor effecting postoperative morbidity is indicated in Fig. 6. Stages of anesthesia after the classification of Guedel were used.[3] The planes shown in the graph are of the third stage. When using cyclopropane, the differentiation of Planes 3 and 4 was impossible. The latter plane of anesthesia was then considered to be that degree of narcosis where respiration was entirely passive or accomplished by the anesthetist. This corresponds to Stage 4 in Guedel's classification. The most profound degree of narcosis during the operation was considered as the plane of anesthesia for that case. Planes 1 and 2 were, of course, more often used for superficial operations, but many serious procedures such as central nervous system, thyroid and kidney operations were invariably done with this lighter anesthesia. Although Planes 3 and 4 were more often used for abdominal surgery, there were many of these operations accomplished in Plane 2. The individual preference of the surgeon was most often the anesthetist's guide to the depth of anesthesia required. When subarachnoid block was accomplished without disturbance of intercostal activity, the per cent of postoperative respiratory complications was less than one-half that found when the anesthesia produced intercostal muscle

paralysis. In the latter group, however, were operations inlvoving the upper abdomen.

Figure 7 represents a consideration of the influence of the operating time on respiratory sequellæ. Fifteen per cent of the nitrous oxid anesthesias, 30% of those with ethylene, 32% with ether and 45% with cyclopropane were for 60 minutes or more. Age and sex influenced the incidence of morbidity. Males developed some respiratory complication more often than females, the ratio for 1 year being 1.3 to 1. Infants under 1 year had fewer complications than any age group while adults suffered most often:

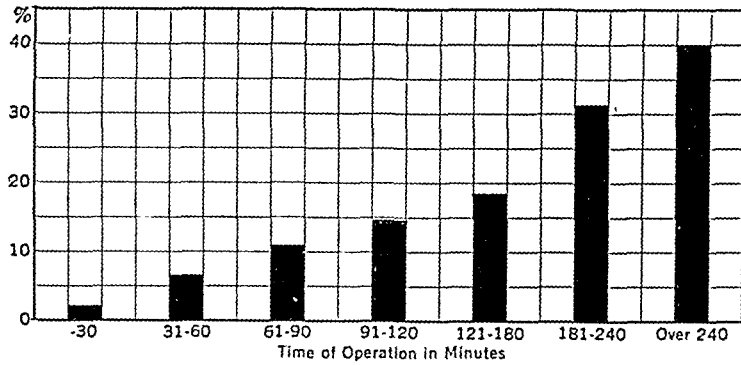


FIG. 7.—All operations were grouped according to the duration. The occurrence of postoperative respiratory complications for each group is graphically represented in percentages.

The statistics in Table 6 were of particular interest to the anesthesia staff since the postoperative morbidity for the individual anesthetists was compared. The contention that the ability, train-

TABLE 6.—COMPLICATIONS FOR INDIVIDUAL ANESTHETISTS COMPARED.

Anesthetist.		Collapse.		Pneumonia.		All respiratory complications.	
No.	Cases.	Ether.	C_3H_6	Ether.	C_3H_6.	Ether.	C_3H_6.
1	934	1.30	0.36	0.77	0.54	7.75	9.2
2	716	1.14	0.00	0.72	0.68	12.70	6.8
3	399	3.60	0.55	0.92	1.10	12.30	9.9
4	655	0.72	0.58	0.72	0.30	8.70	6.1
5	762	2.50	0.33	1.80	0.67	17.80	9.9
6	615	0.85	0.20	0	0.40	2.60	6.0
7	296	0	0	2.40	1.50	9.70	8.6
8	147	0	0	0	0.90	5.50	8.1
9	273	2.80	0.42	0	0.42	5.50	7.1

ing and experience of the anesthetist is the most important factor influencing anesthetic morbidity and mortality is not disproved by these data. In the table, Anesthetist 5 had the larger experience

and was assigned a large number of serious and difficult cases. Many of his anesthesias were given by medical students under supervision. Maintenance and recovery were not always adroitly consummated and this is evident from the data. Anesthetist 1 had more training than any other except 5. Many grave risks were allotted to him; 2, 3, and 6 had a similar amount of training. They were assigned routine cases. Anesthetists 4, 7, 8 and 9 had the least clinical work, but were given good risk cases that were not technically complicated. The results for ether and cyclopropane anesthesias are recorded. Although this table contains data concerning all respiratory complications and specifically pneumonias and collapse, comparable results were registered in the incidence of nausea and emesis and circulatory and other complications.

TABLE 7.—DEATHS FROM RESPIRATORY CAUSES IN VARIOUS SERVICES.

Surgical service.	Total cases.	Respiratory deaths.	
		No.	Per cent.
Orthopedic, minor	889	1	0.1
Herniorrhaphy, ventral and inguinal	407	2	0.5
Vaginal operation	933	2	0.2
Abdominal, lower	992	7	0.7
Ophthalmology	254	1	0.4
Plastic	174	1	0.4
Urology	588	6	1.0
Thoracic	194	6	3.1
Orthopedic, major	578	2	0.4
Ear, nose and throat	494	3	0.6
Abdominal, upper	476	8	1.7
Central nervous system	95	8	8.4
Rectal	235	1	0.4

TABLE 8.—RESPIRATORY DEATHS.

Total cases anesthetized	7874
Total deaths (all causes)	293 (3.72%)
Respiratory deaths	47 (0.59%)

Cause of respiratory deaths.	No.	N_2O.	C_2H_4.	C_3H_6.	Ether.	Proc.	T.B.E.
Pneumonia	31	2	5	9	11	3	1
Collapse	3	0	0	1	2	0	0
Embolus	4	0	0	1	1	2	0
Others	9	3	2	1	3	0	0
Total deaths	47	5	7	12	17	5	1
Total cases	7874	957	974	3103	1696	831	213

Time of death.	O.D.	1–3 P.O.D.	4–7 P.O.D.	2d wk.	Later.
Pneumonia	0	1	8	5	16
Collapse	0	1	1	1	0
Others	1	5	3	2	3
Total	1	7	12	8	19

In Table 7, the respiratory mortality for the series is recorded with the type of operation after which deaths occurred. The cause and time of death as well as the agent used is shown in Table 8. The group listed as "Others" includes aspiration of vomitus, foreign body, pulmonary edema, suffocation, and an accident.

Comment and Summary. It is of course impossible to give in detail all the minor and major respiratory complications found following 7874 operations. Primary attention has been given to anesthesia as contributing to the postoperative morbidity. Although a relatively small number of cases is reported, the data indicate several factors that merit consideration if such morbidity is to be reduced.

The marked seasonal variation is contingent upon the prevalence of respiratory diseases in the population outside the hospital. Other factors appear of less importance. It has been found advisable in this hospital during the months with a high incidence of respiratory infections to omit certain elective operative procedures, particularly plastic operations upon infants.

The presence of any respiratory tract infection, even mild pharyngitis or oral sepsis substantially increases the incidence of postoperative respiratory infections.

The influence of the anesthetic agent was not marked in this series. A careful selection of agents was practiced and comparable morbidity results secured with each.

Anesthesia technique was a more important factor but the incidence of complications more nearly paralleled the surgical procedure involved. When using intermittent analgesia for obstetrics and open drop for tonsillectomies, complications were rare.

The pre-operative risk classification gave the most accurate index of postoperative morbidity expectancy. The increase in respiratory complications was in direct proportion to the seriousness of the risk.

The degree of narcosis distinctly affected the percentage of complications. Evidently surgical procedures that can be well executed with first plane anesthesia should not have more profound narcosis. The training and skill of the individual surgeon will be the determining factor in the degree of narcosis required. Spinal anesthesia without intercostal muscle paralysis accounted for less than one-half as many complications as did the same procedure when the intercostal muscles were paralyzed.

The most striking influence upon postoperative respiratory complications was shown by the duration of operation. Whereas operations lasting 1 hour or less have a morbidity incidence less than the average for the group, the ratio for procedures requiring a longer time increases markedly. When the duration was 1 to 1½ hours, the respiratory complications doubled those of 1 hour. When 2 hours were needed, the percentage of complications was more than 3 times that of 1 hour. In procedures lasting 3 hours, more than

31% of the patients had some respiratory complication. The group requiring more than 4 hours had the highest incidence of respiratory complication. Despite the seriousness of the longer surgical manipulations and the grave risks encountered in the majority of them, duration of operation alone appears to be a definite factor influencing respiratory morbidity.

That the ability, training and experience of the anesthetist modifies morbidity is well shown in these statistics. Teaching students and training anesthetists will be accomplished by an increase in postoperative complications.

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THE LAG PHASE IN EARLY CONGENITAL OSSEOUS SYPHILIS.

A ROENTGENOGRAPHIC STUDY.

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THE value of any diagnostic procedure depends primarily upon its specificity, upon the relative frequency of its occurrence as compared with the total incidence of the disease in question, and upon the time interval necessary for its development after the morbid state is produced. Roentgenologists are universally agreed that the osteochondritis and periostitis which characterize infantile congenital syphilis can, in their typical forms, be confused with no other osseous lesion, and it is the experience of most that nearly 100% will develop bone changes diagnostic of this disease at some time within the first 6 months of postnatal life.[1–6] On the other hand, there seems to be no working criterion by means of which it is possible to determine exactly when the lesions in question are likely to appear in any given case and, since roentgenographic examination is a relatively expensive procedure, it is ordinarily impractical to make repeated Roentgen ray studies until the positive changes finally make their appearance, or until the presence of the disease is satisfactorily ruled out by their failure to develop. An attempt to establish the importance of some of the factors causing these individual variations may prove useful for developing

a rational and at the same time economical approach to the roentgenographic diagnosis of infantile congenital syphilis.

Most roentgenologists and pathologists who have studied the problem of early congenital bone syphilis have been impressed with the fact that the osteochondritis occurring in the metaphyseal growing centers of the bones of syphilitic infants is a phenomenon of fetal and of early postnatal life, and that periostitis in these cases, seldom present at the time of birth, is ordinarily at its height from the second to the fifth months of extrauterine life.[3, 7–10] Péhu, Policard and their associates[4, 5, 11] have especially insisted upon this classification. Exceptions to these general tendencies are common, however, and it is not especially unusual to find syphilitic periostitis in a fetus stillborn at or near term,[5, 12] nor is it uncommon for a syphilitic infant to have roentgenographically normal bones at the time of birth, only to develop diagnostic osseous lesions some few weeks or months thereafter.[3, 8]

The comparative ease with which spirochetes are demonstrated in the syphilitic placenta[13] and in the organs of infants which succumb to this infection[14, 15] would indicate that fetal syphilis is a more virulent disease than is ordinarily encountered in adult life. Whether this massive infection is the result of the repeated transfer of spirochetes from the maternal to the fetal circulation in the placenta over a period of months, whether it arises from rapid multiplication of the microörganism because the resistance of the embryo is low, or whether it is attendant on other circumstances of fetal development, it is probable that these factors just mentioned, since they affect all embryos similarly, have less to do with determining when the bone lesions will appear than has the actual time in intrauterine life in which the infection takes place. The fact that the offspring of syphilitic mothers are ordinarily inaccessible to study for some weeks or months after they have become diseased, has left the question of the duration of the disease in them at the time of birth largely a matter for conjecture. In addition, there is obviously a latent period from the time of spirochetal invasion until the impairment of bone development by the action of these microörganisms at the temporary zones of calcification has become sufficiently marked to affect the roentgenograph. An attempt to determine, as accurately as possible, this lag phase is the primary object of this study. For it is self-evident that if the latent period from the time of spirochetal invasion until the bone lesion becomes roentgenographically manifest is known, the approximate duration of the syphilitic infection in the child may be estimated with a reasonable degree of certitude. We have endeavored to attack the problem from several angles, checking one result against another in an effort to determine whether they coincided sufficiently to warrant any definite conclusions. Since the living human fetus cannot be studied adequately prenatally, the evidence brought

forth must be, in part at least, inferential, if the question is to be clarified at all.

In this connection, attention should be directed toward the work of Alexander[16] and Harris,[17] Klaften and Priesel,[18] the greater part of which we have been able to confirm. The former 2 observers pointed out that it is possible, in certain instances at least, where syphilitic osteochondritis is present at the time of birth, to estimate the approximate month in fetal life at which the first recognizable bone lesion appeared, by assuming that impaired osseous development results from then until the time of birth and by measuring the width of this bone scar on the diaphysis (Fig. 6). The latter investigators attempted to estimate the duration of the bone lesion at the time of birth in the offspring of partially treated syphilitic mothers, utilizing the apparent fact that, if the child is infected before prenatal treatment is commenced, the bone development proceeds more or less normally after the onset of therapy, leaving bands of sclerosis, vestiges of the antecedent active infection on the shaft of the bones at varying and easily measured distances from the metaphyses.

Material. Our material consists of 252 complete roentgenographic studies performed on the offspring of 131 syphilitic pregnancies which occurred in the Philadelphia General Hospital between December 1, 1933, and June 15, 1935. Each mother was carefully studied from the standpoint of this disease prenatally and postnatally, and the majority of the children were followed for a matter of several months, or at least long enough to confirm the roentgenographic studies by clinical and blood serologic examination. Few of the children received any antisyphilitic therapy during the period of observation, so the roentgenographic picture obtained resulted for the most part from the syphilis alone and was not the outcome of the combined changes produced by syphilis and therapy. The group of cases followed by serial studies is further highly selected in that only the infants who received little or no prenatal therapy and whose mothers were proven to have active early syphilis with strongly positive serologic reactions were considered. Accordingly, about one-half of the 258 syphilitic deliveries which occurred in the hospital in this period of time was thought suitable for the purposes of this study. The sole idea in thus selecting the cases was to obtain as high as possible a number of diseased children and thus of positive roentgenographs.

The Fetus is Apparently Infected in the Latter Half of Pregnancy. As a preamble to the report of the actual results obtained, it is of considerable interest and importance to note what can be gleaned from the literature regarding the earliest recognizable fetal bone changes as compared with the earliest demonstrated syphilitic spirochetosis. Clinical and pathologic studies have indicated that syphilitic miscarriage is uncommon, if indeed it occurs at all, prior

to the 16th week of pregnancy.[19] For instance, it has been shown that spontaneous abortion (*i. e.*, miscarriage prior to the 4th month) is of no greater frequency among syphilitic than it is among non-syphilitic mothers. Similarly, late miscarriage has a noticeably greater incidence among known syphilitic patients. Prenatal antisyphilitic therapy which, according to the best authorities,[20, 21] exerts its beneficent action principally by preventing the transplacental transfer of spirochetes and not so much by treating an already infected fetus, can assure the birth of a healthy infant in almost 100% of cases if it is continued throughout the latter half of pregnancy only.[22, 23, 24] Gräfenberg,[25] who has carefully studied the bacteriology of fetal syphilis and whose work has been confirmed by many European investigators and generally accepted,[7–10, 26] states that he could discover no embryo which contained spirochetes prior to the 16th week of fetal life.

Assuming then, as seems justified, that the earliest fetal infection dates from the beginning of the 5th lunar month, let us see when, in embryonal life, syphilitic bone changes can first be recognized roentgenographically. Fraenkel[12] was able to show a definite osteochondritis by this means in a 26 cm. fetus; Alexander[16] discovered early osseous changes in fetuses 26.5, 27.5 and 28 cm. in length. A 26 cm. fetus is in its 6th lunar month of intrauterine life, 21 to 22 weeks old.[27, 28] Syphilitic bone changes have, apparently, never been demonstrated roentgenographically in fetuses younger than this. According to Fraenkel's comprehensive studies,[12, 29] the fetal periostitis may begin to become evident roentgenographically in 42 to 43 cm. fetuses, namely, in those which are 32 to 34 weeks old. Harris', Alexander's, and Klaften and Priesel's studies with older stillborn fetuses or with living infants indicate that the earliest bone changes date from the 6th lunar month of intrauterine life. The presumptive evidence, therefore, would seem to indicate that osteochondritis becomes recognizable roentgenographically 5 to 6 weeks following fetal infection and that about 16 weeks are necessary for the development of a manifest early periostitis.

A Syphilitic Child Born of a Mother Infected Late in Pregnancy. Another method of determining the approximate period in intrauterine life in which the fetus is infected is by selecting for study mothers who are infected and who develop signs of primary or secondary syphilis in the later months of pregnancy. Spirochetemia is at its height at about the secondary stage of the disease, so that a pregnant woman who develops clinical early syphilis close to term will, presumably, infect her offspring very quickly and readily, if she is permitted to go untreated. That mother who acquires her disease closest to the time of birth of her child and whose offspring shows, at the same time, an early osteochondritis when delivered, will give a fairly accurate measure of the time required for this diagnostic sign to appear in the roentgenograph.

Of the 258 syphilitic deliveries which occurred in the Philadelphia General Hospital during the period of this study, 17 fall into this classification. They are summarized in some detail in Table 1. Two of the offspring were stillborn and 1 died in less than 24 hours; these were not studied roentgenographically. Of the living children, 5, those who had received considerable prenatal treatment, were clinically and roentgenographically normal; 2 of the infants were not adequately followed. The remaining 7, born 4, 9, 12, 15, 16, 18 and 23 weeks, respectively, after the onset of clinical symptoms in the mother, all showed syphilitic osteochondritis on their first postnatal Roentgen examination (Figs. 1 and 2). In Case 256, the mother had been infected for about 8 weeks only and the child, presumably, for something over a month before the roentgenograph was performed. This type of evidence, therefore, would indicate that about 5 weeks are necessary for the development of Roentgen-positive bone syphilis.

TABLE 1.—ROENTGENOGRAPHIC DIAGNOSIS IN INFANTS WHOSE MOTHERS DEVELOPED PRIMARY OR SECONDARY SYPHILIS LATE IN PREGNANCY. THE LAG PHASE IN THESE CASES IS SHOWN TO BE ABOUT 5 WEEKS.

No.	Type of syphilis in mother.	Date of onset of clinical symptoms in mother.	Date of delivery.	Child born.	Prenatal treat. (weeks).	Wassermann (At birth) Mat.	Wassermann (At birth) Cord.	Date appearance congenital bone syphilis.
49	Papular secondary	8/ /34	2/13/35	Dead	None	4+	4+	
64	Genital condylomata	1/ 9/34,	3/19/34	Dead	4	4+	4+	
162	Papular secondary	7/ 5/34	10/ 6/34 (Lived less than 24 hrs.)	Alive	3	4+	4+	
20	Genital primary	8/10/34	12/11/34	Alive	10	Neg.	Neg.	Child not syphilitic
55	Maculopapular secondary	6/25/34	1/16/35	Alive	23	3+	Neg.	Child not syphilitic
62	Genital condylomata	6/ 7/34	11/12/34	Alive	10	4+	Neg.	Child not syphilitic
101	Maculopapular secondary	4/15/34	8/21/34	Alive	11	Neg.	Neg.	Child not syphilitic
213	Annulopapular secondary	1/15/34	6/13/34	Alive	11	4+	1+	Child not syphilitic
83	Genital primary Papular secondary	11/27/33	2/24/34	Alive	7	2+	Neg.	Not Roentgen rayed
119	Annulopapular secondary	9/24/34	3/ 3/35	Alive	7	Neg.	Neg.	Child not followed
256	Genital primary	4/15/35	5/13/35	Alive	None	1+	Neg.	5/20/35 (Early osteochondritis)
21	Maculopapular secondary	3/15/34	4/14/34	Alive	None	4+	4+	5/25/34 (Early osteochondritis)
52	Maculopapular secondary	12/24/34	3/20/35	Alive	12	Advanced periostitis Neg.	Neg.	9/18/34 3/27/35 (Osteochondritis)
102	Genital primary Annulopapular secondary	12/26/33 12/21/34	6/13/34	Alive	8	1+	Neg.	6/20/34 (Osteochondritis)
188	Genital primary Papular secondary	8/24/33	12/23/33	Alive	6	Advanced periostitis Neg.	Neg.	9/25/34 12/29/33 (Osteochondritis)
17	Genital primary	8/15/33	12/ 2/33	Alive	1	4+	Neg.	12/8/33 (Osteochondritis)
160	Papular secondary	2/15/34	7/27/34	Alive	6	Neg.	Neg.	8/2/34 (Osteochondritis)

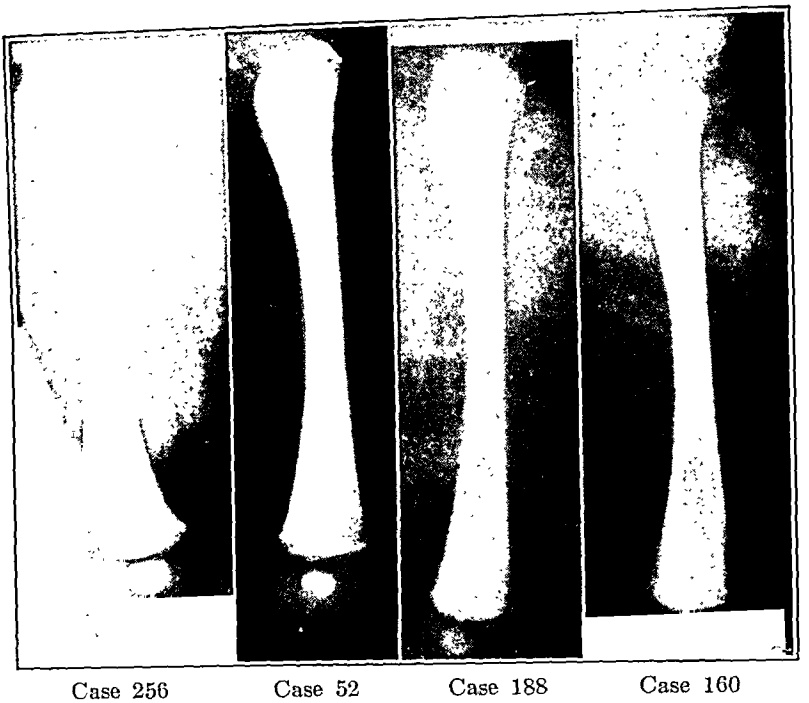
Osteochondritis Not Present at the Time of Birth Develops Postnatally. Further evidence can be obtained concerning this lag phase by selecting those cases in which a syphilitic child is born with no demonstrable osseous lesion, but in which Roentgen evidence of bone

involvement develops postnatally. This was true in the 16 cases in our series which are summarized in Table 2. All of these mothers had latent syphilis. Obviously, since about 20% of the offspring of untreated mothers with active syphilis fail to contract the disease,[23, 24, 30, 31] in spite of 9 months of indirect exposure to the mother's blood and tissues while they are *in utero*, infection of the embryo may occur right up until the time of delivery. A fetus infected before birth will develop bone changes sooner postnatally than the infant infected at the time of birth, the latter having the longest postnatal interval before osseous changes are demonstrable. Casazza[7] has pointed out that syphilitic osteochondritis is seldom seen after the 3d or 4th months of extrauterine life, but no effort, apparently, has been made to discover exactly how long after birth the earliest changes could be detected, though Schneider[8] had 1 case which showed a rather early metaphyseal lesion at the age of 2 months. The first 6 cases in Table 2 showed their early osteochondritic changes at 4 (4×), 5 and 6 weeks, respectively. This would indicate that it takes no less than 4 weeks and no more than 6 weeks ordinarily for the first bone changes to develop.

TABLE 2.—OSTEOCHONDRITIS NOT PRESENT AT THE TIME OF BIRTH BUT BONE CHANGES APPEAR LATER. DURATION OF TIME POSTNATALLY UNTIL THE DEVELOPMENT OF THESE OSSEOUS LESIONS. ALL CHILDREN BORN ALIVE OF MOTHERS WITH LATENT SYPHILIS.

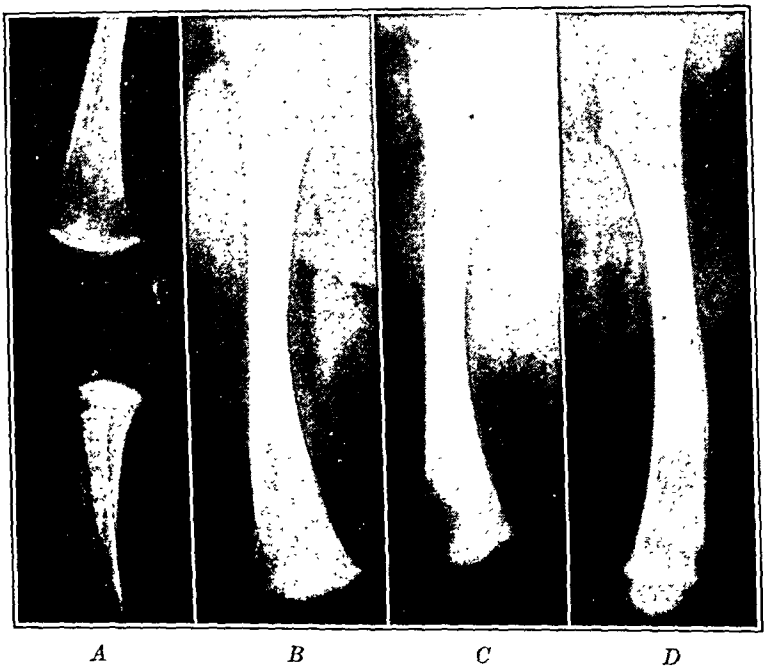
No.	Date of birth.	Date when roentgenograph became positive.	Weeks postnatally when positive roentgenograph was discovered.	Type of bone change.	Prenatal treatment (weeks).	Child's clinical symptoms.	Wassermann at time of delivery. Mat.	Wassermann at time of delivery. Cord.
72	7/25/34	8/28/34	4	Osteochondritis	3	None	1+	Neg.
109	7/22/34	8/21/34	4	Osteochondritis	1	Lymphadenopathy	3+	Neg.
121	12/ 4/34	1/15/35	6	Osteochondritis	2	Gen. lymph.	4+	2+
		2/19/35	10	Periostitis	..	Palp. spleen		
163	9/17/34	10/23/34	5	Osteochondritis	8	Snuffles	3+	Neg.
		11/20/34	9	Periostitis	..	Syphiloderm, palp. liver and spleen		
1	5/15/34	6/15/34	4	Osteochondritis	0	Snuffles	3+	Neg.
		10/ 9/34	20	Adv. periostitis	..	Gen. lymph.		
132	12/14/33	1/15/34	4	Osteochondritis	0	Snuffles	4+	?
		4/19/34	26	Adv. periostitis	..	Syphiloderm, palp. liver and spleen		
208	11/18/34	1/15/35	8	Early periostitis	16	Snuffles	4+	Neg.
211	5/23/34	7/17/34	8	Early periostitis	13	Snuffles, splenomegaly	1+	Neg.
232	9/ 1/34	10/30/34	8	Periostitis	4	Snuffles	Neg.	Neg.
147	1/23/35	3/26/35	9	Osteochondritis, periostitis	4	Snuffles	3+	Neg.
251	3/ 8/34	5/21/34	10	Periostitis	5	None	4+	4+
183	9/16/34	12/16/34	12	Osteochondritis, periostitis	13	None	1+	Neg.
61	7/ 6/34	10/ 4/34	12	Periostitis	7	None	4+	Neg.
181	2/13/34	5/22/34	13	Osteochondritis, periostitis	13	None	Neg.	Neg.
202	6/22/34	9/25/34	13	Periostitis	9	Snuffles	2+	Neg.
218	1/19/34	5/ 3/34	14	Periostitis	11	Child died, syphilis, 5/6/34	1+	3+

In Case 121 periostitis was demonstrated only 4 weeks after the osteochondritis became manifest. This may indicate that the latter change should have been recognized earlier, possibly even at the time of birth. Case 163 (Fig. 3) falls into a similar category, for here, although diagnostic bone changes did not develop until



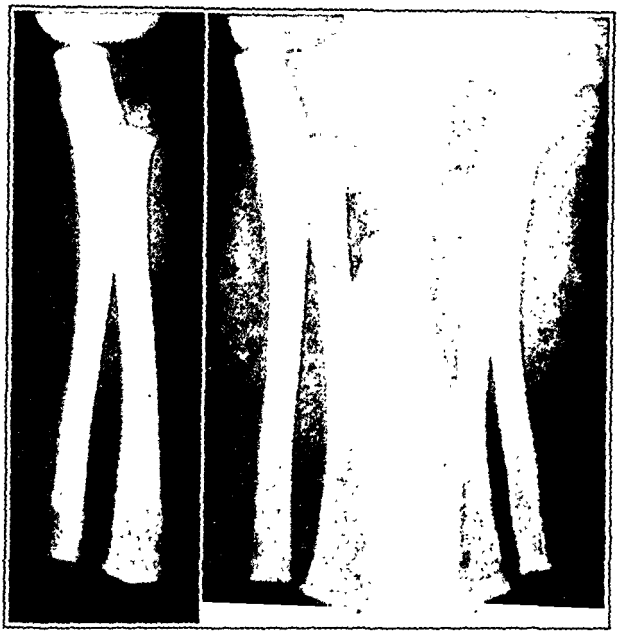
Case 256 Case 52 Case 188 Case 160

FIG. 1.—Early syphilitic osteochondritis in distal femoral metaphyses, at the time of birth, in infants whose mothers contracted syphilis late in pregnancy. Note the narrow band of sclerosis with slight submetaphyseal rarefaction in each instance.



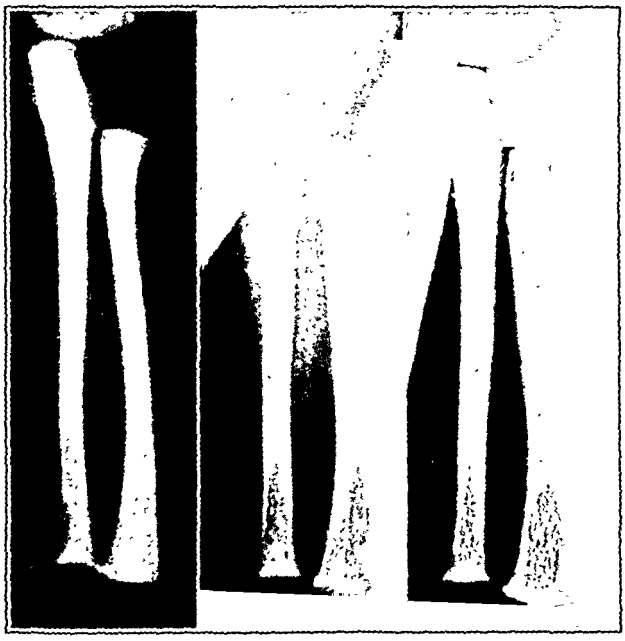
A *B* *C* *D*

FIG. 2.—Cases 21 (*A* and *B*) and 102 (*C* and *D*) showing early osteochondritis and later periostitis in femora; the mothers contracted syphilis late in pregnancy. The osteochondritic change shown in *A* is when the infant was 5 weeks old. Note marked metaphyseal sclerosis in all the long bones shown, with beautiful zone of submetaphyseal rarefaction and second zone of increased density shown in proximal tibia. *B* is at the age of 5 months with marked periostitis on the outer aspect of the diaphysis. Diaphyseal rarefaction is clearly shown in *C* at 6 days and *D* at 3 months. The latter shows, in addition, periostitis.



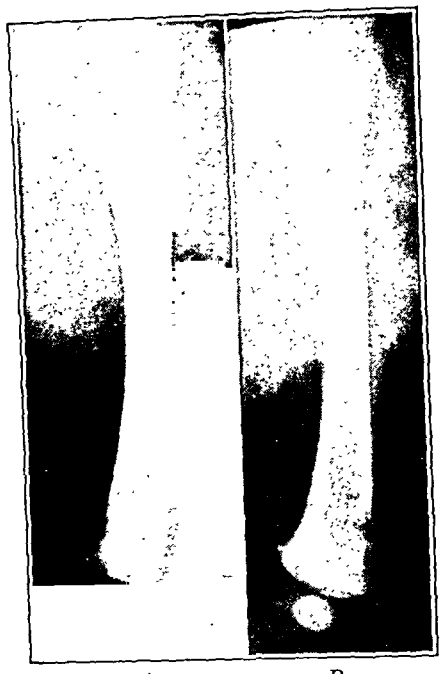
A B C

FIG. 3.—The development of syphilitic osteochondritis and periostitis postnatally. *A* shows the radius and ulna at 6 days with no more than normal metaphyseal sclerosis; *B*, *the child is 1 month old. There is a definite zone of sclerosis in the distal* radial and ulnar metaphyses with a zone of submetaphyseal rarefaction and a second *poorly defined band of sclerosis.* *C*, the metaphyseal sclerosis has increased and there is an early periostitis, best seen on the inner aspect of the shaft of the ulna and on the outer aspect of the shaft of the radius.



A B C

FIG. 4.—Case illustrating the fact that it takes several weeks for syphilitic osteochondritis to reach its height. *A*, when the child is 6 days old, the metaphyseal sclerosis is scarcely discernible; *B*, at the age of 1 month, the band has greatly increased in width, while *C*, at the age of 2½ months, there is in addition some flaring of the metaphyses with a tendency toward spur formation.



A B

FIG. 5.—The time interval between the appearance of syphilitic osteochondritis and syphilitic periostitis in the roentgenograph. This is Case 190 which showed early osteochondritis in the distal femoral metaphysis, *A*, at the time of birth. By the age of 11 weeks, *B*, the metaphyseal sclerosis has become more marked and an early but definite periostitis is present on the outer aspect of the diaphysis.



A B

FIG. 6.—Marked diaphysitis in the femur and tibia produced by prolonged action of the syphilis spirochete in the temporary zones of calcification. In *A*, the infant was 6 days old, the syphilitic infection dating in all probability from the 6th month of pregnancy. *B*, a similar picture in a 10-month-old infant. This is Case 188, the early osteochondritis of which is shown in Fig. 1. The infant received a small amount of treatment postnatally but was lost sight of for several months, to return for observation with the peculiar osseous picture illustrated.

the infant was 5 weeks old, there was a questionable osteochondritis at the time of birth, indicating that the infection *in utero* had probably occurred earlier than we had originally calculated. The fact that it took Cases 1 and 132 16 and 22 weeks, respectively, to develop moderately advanced periostitis would indicate that several months are usually consumed in forming this Roentgen picture. More accurate information can be obtained concerning this latent interval from a careful study of the remaining cases in Table 2 and from those summarized in Table 3, in which osteochondritis was present at the time of birth but in which the lapse of time necessary for the development of periostitis has been accurately determined.

The Latent Interval Necessary for the Development of Syphilitic Periostitis. The last 10 cases in Table 2 summarize the instances in which early periosteal changes were discovered postnatally, no bone changes being present in the roentgenograph at the time of birth. The longest time interval necessary for the development of an early periostitis will indicate the child infected closest to the time of birth, in this series the latent interval being 12 to 14 weeks. In other words, periostitis appears, presumably, between 3 and 4 months after the child is diseased.

TABLE 3.—OSTEOCHONDRITIS PRESENT AT THE TIME OF BIRTH. LAPSE OF TIME UNTIL PERIOSTITIS DEVELOPED; UNTREATED CASES.

No.	Date of birth.	Date when periostitis was discovered.	Weeks postnatally that periostitis developed.	Prenatal treatment (weeks).	Child's clinical symptoms.	Wassermann at time of delivery. Mat.	Wassermann at time of delivery. Cord
117	8/ 5/34	9/27/34	7	1	Child died cong. syph., 5/3/35	4+	Neg.
129	8/18/34	10/ 9/34	8	2	Gen. lymph., palp. liver and spleen	1+	Neg.
10	1/20/34	3/19/34	8	1	None	3+	Neg.
247	4/11/34	6/ 7/34	8	8	Snuffles, syphiloderm, gen. lymph.	3+	Neg.
118	1/23/34	3/22/34	8	1	None	Neg.	Neg.
35	1/13/35	3/21/35	9	None	Pseudoparalysis of Parrot	Neg.	Neg.
137	10/ 1/34	12/ 9/34	10 (early)	11	None	4+	Neg.
190	1/30/34	4/23/34	11 (early)	9	Gen. lymph., hepatomegaly	2+	Neg.
112	1/29/34	4/23/34	11 (early)	8	None	1+	Neg.
82	2/28/34	6/12/34	14 (definite)	2	Snuffles, gen. lymph., splenomegaly	Neg.	Neg.
28	12/14/33	4/ 2/34	15 (advanced)	8	None	4+	Neg.

Now turning to Table 3, and assuming again that the longest time interval before the development of periostitis indicates the child infected closest to the time of birth, and excluding Cases 28 and 82, in which the periostitis when discovered was moderately advanced, the longest osteochondritic-periosteal interval is 10 to 11 weeks (Figs. 4 and 5). This indicates again that periostitis develops some 2 to 3 months after the osteochondritis appears and some 4 months after the child is infected.

These results coincide rather well with the ideas portrayed in the

theoretical discussion which preceded the description of our actual findings: namely, if syphilitic fetuses stillborn at or near term comprise those embryos which have been infected earliest in the pregnancy, the periostitis which occurs not uncommonly in such offspring would indicate that they become diseased ordinarily about 4 calendar months before birth or in the 5th month of intrauterine life. Since the children born alive, on the other hand, do not ordinarily show periostitis until several weeks postnatally, such infants probably become diseased in the still later months of pregnancy.

Summary. Even though it has been realized for some time that considerable information could be derived concerning the duration of an osseous lesion produced by congenital syphilis from a roentgenographic study of the extent of the impairment of bone development after the lesion first became detectable, the fact that the latent interval between the time of fetal infection and the development of the earliest demonstrable osteochondritic and periosteal changes was unknown, left the actual duration of the disease in the infant a matter largely for speculation. We realize that the extent of the lag phase may be, and in some instances probably is, governed by a number of interplaying factors, but we have been impressed, as have a few other workers who have studied congenital bone syphilis by means of serial roentgenographs, with the almost mathematical time precision with which these lesions become manifest. By a study of the time interval alone, the majority of the individual variations found in comparing one case with another can apparently be explained; the few exceptions are probably caused by the addition of other elements, the relative importance of which remains to be determined (Fig. 6). Nonetheless, we feel that we may assume, with a reasonable degree of accuracy, that syphilitic osteochondritis, all other things being equal, becomes roentgenographically manifest about 5 weeks after the fetus is infected, while syphilitic periostitis requires approximately 4 months to develop.

It should be apparent, therefore, that the roentgenographic diagnosis of congenital syphilis, to be of its greatest value, must rest upon the recognition of syphilitic osteochondritis, for, by the time periostitis has developed, the child has been infected for several months, usually exhibits clinical signs of the disease, and has ordinarily become seropositive.* A single roentgenogram performed when the infant is 6 weeks old should detect almost every case, though osseous lesions could be discovered sooner in many instances, were not repeated roentgenographic studies inhibited by their expense.

* The unreliability of the blood serologic test as an absolute diagnostic criterion of congenital syphilis in the first few weeks of life is well recognized. In an article entitled, "Roentgen Positive, Sero-negative Infantile Congenital Syphilis," soon to appear in the Am. J. Dis. Child., we have indicated the value of roentgenographic examination in these seronegative, and otherwise undiagnosable cases.

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THE MINOR BLOOD AGGLUTININS AND THEIR RELATION TO POST TRANSFUSION REACTIONS.

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The minor hemagglutinins (the subgroup isoagglutinins; Landsteiner's irregular isoagglutinins and normal cold agglutinins; the pathologic cold agglutinin; and the rouleau forming property) have

been the subjects of several interesting studies.[1–9] Very little effort, however, has been made to determine their practical importance in relation to the transfusion of blood. Landsteiner and Levine[2] report 6 transfusions without reaction with bloods showing minor incompatibilities at 20° C. Manheims and Brunner[11] report a transfusion without reaction in an individual with autoagglutinin, and Sherman[11] records two such instances. Tiber[12] considers the intra-group incompatibilities insufficient to cause death. Kramer[13] recounts 10 cases of autoagglutination with a severe reaction in 1. Brewer[14] finds auto- and cold agglutinins the most frequent cause of incompatibility between patients' serum and donors' cells, and attributes reactions to them. Unger[15] noted sharp reactions when minor incompatibilities existed in the cross tests.

The sub-group isoagglutinins, the irregular isoagglutinins, and the normal cold agglutinins are not clearly defined, but merge one into the other, and are more frequently encountered and more active at low temperatures. Landsteiner states that practically all human sera agglutinate their own cells at 0° C. The pathologic cold agglutinin (autoagglutinin) does not differ clearly from the normal cold agglutinin, except that it is often of high titer and is associated with pathologic states. It seems reasonable to suppose that it is really the normal cold agglutinin increased in strength by some process of disease. At any rate minor agglutinins effective on the cells of the same individual and others of the same blood group (and on those of group 0) at low temperatures (10° to 0° C.), but not at high temperatures, comprise the majority of the minor agglutinins.

Autoagglutinin is characterized first by the fact that its property of clumping erythrocytes is entirely wanting at 37° C., but becomes increasingly effective as the temperature is lowered, being maximal at 0° C. At, or near, this temperature the agglutinin is fixed to the cells which become drawn into masses. As the temperature is elevated, the reaction is reversed, the agglutinin becoming detached and the cells "unclumped." This is a property of the serum, not of the cells. Furthermore, this is not a specific agglutinin, but one capable of acting on the red cells of many, possibly all, animals (panagglutinin). It is, nonetheless, a true agglutinin, being absorbable, and, apparently, not affected by lecithin. A few authors, however, believe it to be related to the rouleau forming property. This latter is not attributed to a true agglutinin, but rather to a physiochemical property of the serum related to surface tension. It is not removed by absorption, and is inhibited by lecithin. It does, however, draw cells into masses which can be confused with those of true agglutination.

The present study was undertaken after an experience in which failure to detect a strong autoagglutinatinin in a patient's serum resulted in a very severe post-transfusion reaction. A review of the

literature lent support to the idea that the minor agglutinins were probably of importance, although no conclusive evidence of this had been produced. I therefore decided to perform routine cross agglutinations according to the method here described with the hope of securing evidence bearing on this question.

Technique. The procedure here employed is as follows: Venous blood collected in sterile test tubes is allowed to clot at 37° C., or if previously chilled, is warmed to 37° C. After removal from the incubator, serum is promptly centrifuged and pipetted off to prevent any but slight chilling. The cells are collected in 1.5% sodium citrate in normal saline (or other suitable fluid) and washed twice in saline warmed initially to 37° C. These steps assure a maximum of autoagglutinin in the serum and its removal from the cells. On clean glass microslides ringed with a wax pencil the following mixtures are prepared: patient's serum and patient's cells, patient's serum and donor's cells, donor's serum and donor's cells, donor's serum and patient's cells. The suspensions are light, about 1%, as an excess of cells masks agglutination.[16] The slides are placed in the refrigerator (5 to 10° C.) for 30 minutes, then removed, one at a time, gently agitated and observed at once under the scope. Agglutination is recorded as from 0 to +4. A second observation is made after about 10 minutes at room temperature (or 37° C.) to note reversal of agglutination. The following is an example of the application of the technique from my protocols:

Patient's serum plus patient's cells +4
Patient's serum plus donor's cells +4
Donor's serum plus donor's cells 0
Donor's serum plus patient's cells 0

"Agglutination in patient's serum completely disappeared after 10 minutes at room temperature; no rouleaux. Diagnosis—strong autoagglutinin in patient's serum. Advise no more than 100 cc. blood be given at one time."

This technique detects incompatibilities due to both major and minor agglutinins, including the autoagglutinin. This latter is missed by the usual technique in which clots are allowed to become chilled, and serum-cell mixtures are incubated at room temperature.

During the period of the work here reported I was under the impression that microscopic inspection alone would clearly differentiate rouleau clumping, as claimed by Coca.[17] More recent experience has led me to believe, however, that this is not always a reliable method, for when autoagglutinin and the rouleau forming substance are present in the same serum, each appears to interfere with the characteristic behavior of the other. When in doubt, lecithin should be used, as suggested by Lattes.[18] One or two platinum loop-fulls of a rather heavy suspension in normal saline are mixed with the serum-cell suspension, which is then returned to the refrigerator for 30 minutes. Since lecithin was not used in this study, the reactions here recorded may represent some instances of rouleau clumping, although probably most are those of autoagglutination. I was also under the impression that a +4 slide reaction indicated an agglutinin of high titer. Again I have found, however, that such a reaction may be produced in undiluted serum with an

actual titer of no more than 1 to 4, or 1 to 8. Consequently, the +4 reactions here recorded do not necessarily indicate high titers.

This study of the minor blood agglutinins includes 161 sera from 130 patients, and 265 sera from as many presumably healthy donors (Chart I).

CHART I.—INCIDENCE OF AUTOAGGLUTINATION IN ILL AND HEALTHY SUBJECTS.

Agglutination.	Patients' Sera.	Patients' %	Donors' Sera.	Donors' %
0	61	38.0	104	39.3
+1	24	14.9	66	24.9
+2	39	24.2	69	26.0
+3	18	11.2	16	6.0
+4	15	9.3	4	1.5
Sub-groups	4	2.5	6	2.3
	161		265	

Four patients' sera and 6 donors' sera were found which contained no autoagglutinin, but which agglutinated the cells of one or more individuals of the same blood group. All of these were Group II sera and doubtless represented examples of the sub-group II. One such serum agglutinated the cells of 5 Group II individuals strongly (+3), of another weakly (+1), and of 3 others not at all.

Fifty-nine per cent of sera of both donors and patients had more or less power to agglutinate their own cells and the cells of others of the same group, while incompatibilities not associated with autoagglutination occurred in only about 2.5% of sera. Thus autoagglutination seems to account for the great majority of intragroup incompatibilities. While this type of reaction is equally common in donors and patients, and doubtless represents Landsteiner's normal cold agglutinins, the +3 reactions were twice as frequent, and +4 reactions 6 times as frequent in the sick as in the healthy subjects. This observation has its greatest interest in the implication that the normal cold agglutinins are often increased in titer by the processes of disease; and indicates that, in an average series of patients in need of transfusion, 1 in 5 will have in his blood an autoagglutinin of sufficient strength to make a post-transfusion reaction a probability.

Medical literature associates autoagglutinins (pathologic cold agglutinins) most often with hemolytic anemias, some forms of cirrhosis of the liver, paroxysmal hemoglobinuria, trypanosomiasis, and repeated transfusions (in rabbits). In this series the condition was most frequently associated with infections by hemolytic streptococci and staphylococci. One patient had had a ruptured ectopic pregnancy, and another was absorbing a large hematoma. It would appear, therefore, that the destruction of blood within the body is an important factor in the development of a strong autoagglutinin. This suggests the development of an antibody against the red cells of the same species, and even of the same individual. However,

this agglutinin is not a specific one, but one capable of acting on the red cells of many animals. Kramer suggests that auto-lipoid antibodies are developed in such instances, which react with the lipoids of the erythrocytes. Mino believes that under certain conditions of non-specific stimulation the body produces antibodies in excess, including the panagglutinin. Landsteiner's and Kettle's reports of weak cold agglutinins in practically every human blood supplement this idea. Belk[19] has furnished evidence of the same sort in a case of infectious mononucleosis.

It was hoped that this study would show conclusively that post-transfusion reactions are caused by, or are associated with, auto-agglutinins. In 209 transfusions, practically all by the citrate method, performed on 82 patients, there were 23 reactions (11%). Of these, 3 were apparently due to cardiac embarrassment, 1 to allergy, and 1 to incipient coagulation of the donor's blood. Two other reactions occurred with perfect cross tests, and seemingly should be attributed to technique, although every care was taken to avoid dirty apparatus, over-heating or chilling of the blood, and improperly made saline.[21] The desirability of a spray trap in the still was not known to me at the time this work was done, and this may have been a factor in the reaction. I believe, however, that conclusions drawn later are still justified. The typing sera were frequently checked, and in no instance was an error made in the blood group of patient or donor. This leaves 16 reactions (70%) for which there was no apparent cause except blood incompatibility due to autoagglutinins which were demonstrated prior to transfusion in 100% of this group. When individual cases are considered, the impression is obtained that smaller quantities of blood produced reactions in those with strong autoagglutinins, amounts of 110 and 115 cc. having been followed by reactions in the former, while no reaction occurred in any patient with a weak autoagglutinin unless 250 cc. or more, of blood was given. In a few instances repeated transfusions with increasing amounts of blood resulted in a reaction after the final and larger amount.

Proof positive of the relation between autoagglutinin and post-transfusion reaction was not developed, however, as reactions were not found to be more frequent in those with strong agglutinins. This observation is modified by the fact that the amount of blood given each individual was determined in advance by the degree of incompatibility as shown by the cross test, and patients whose serum showed +3 and +4 autoagglutination were either not transfused at all, or only with small amounts. I did not feel justified in giving such patients 400 to 500 cc. of blood. Had this been done, it is possible that a high per cent of reactions would have resulted in this group, and so clear proof of the rôle of the autoagglutinin in this connection have been furnished.

The suggestive evidence that agglutinins are productive of post-

transfusion reactions lies in these observations: 1, The incidence of reactions was quite low in this series in which the decision as to transfusion and the amount of blood to be given was based on the presence of autoagglutinin in the patient's serum; 2, the only apparent cause for 70% of the reactions was the presence of autoagglutinin in the patient's blood; 3, smaller amounts of blood seemed capable of producing post-transfusion reactions in patients whose serum contained a strong minor agglutinin than in those with a weak agglutinin; 4, in a few instances repeated transfusions with increasing amounts of blood resulted in a reaction after the last and largest amount only (Chart II).

CHART II.—HEMOLYTIC STREPTOCOCCUS SEPTICEMIA FOLLOWING ABORTION. AUTOAGGLUTINATION +4. MRS. M.

	Transfusion.	Reaction.
Morning	100 cc.	0
Noon	135 cc.	0
Evening	250 cc.	+

With the usual method of blood matching transfusion reactions are rather frequent, even when satisfactory donors are found. This had led to the practice of giving small repeated transfusions in the hope of avoiding these reactions. I am sure that there is little virtue in small transfusions as such, the chief reason for their use being the fact that large amounts are dangerous in some cases because of blood incompatibilities, or a weak circulation. Any adult in need of blood will usually need 400 to 500 cc., and it is less annoying to patient, physician and donor to give this in one operation, if this can be done safely. I feel that a method of donor selection which demonstrates minor agglutinins has this advantage, that it permits a rational, rather than an arbitrary selection of patients for small transfusions. It enables one to avoid over-doses of blood in those who probably can tolerate only small amounts (those with minor agglutinins), and under-doses in those who can safely be given 400 cc. or more. Very large quantities of blood in small repeated doses can, however, be given safely to patients with strong minor agglutinins, and if the first few injections be cautiously increased in amount, the tolerance of the individual can be determined without greatly overstepping it (Chart III).

Another practical consideration is this: Strong incompatibilities due to autoagglutinins (pathologic cold agglutinins) most often appear as a clumping of the donor's cells by the patient's serum. Now it is clearly shown that this is a property of the serum, not of the cells. Consequently, it is useless to test a succession of donors in the hope of finding one suitable, *when positive auto- and cross-tests* with the patient's serum show that the element of incompatibility lies there. Such a serum will similarly agglutinate the cells of all donors (with minor quantitative differences). What is

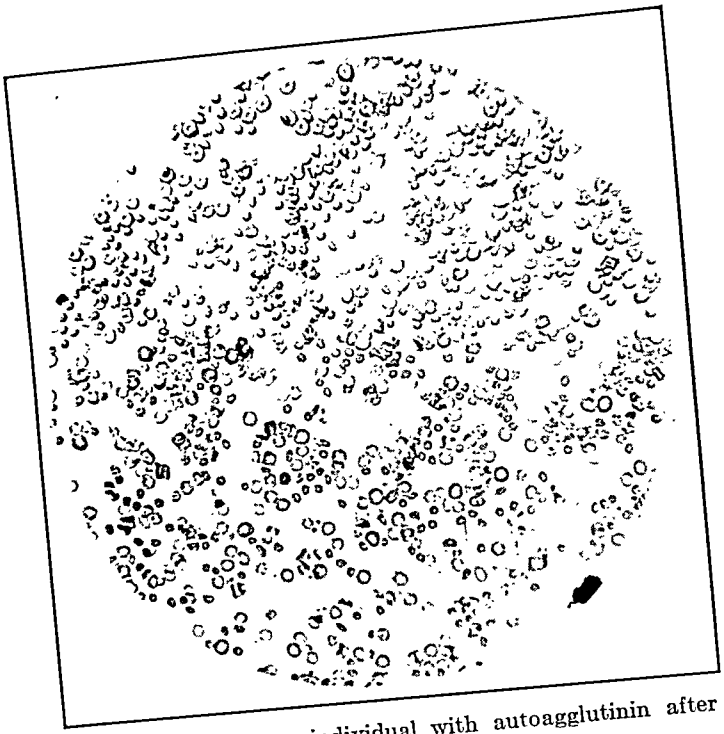


FIG. 1.—Serum and cells of an individual with autoagglutinin after 30 minutes at 20° C.

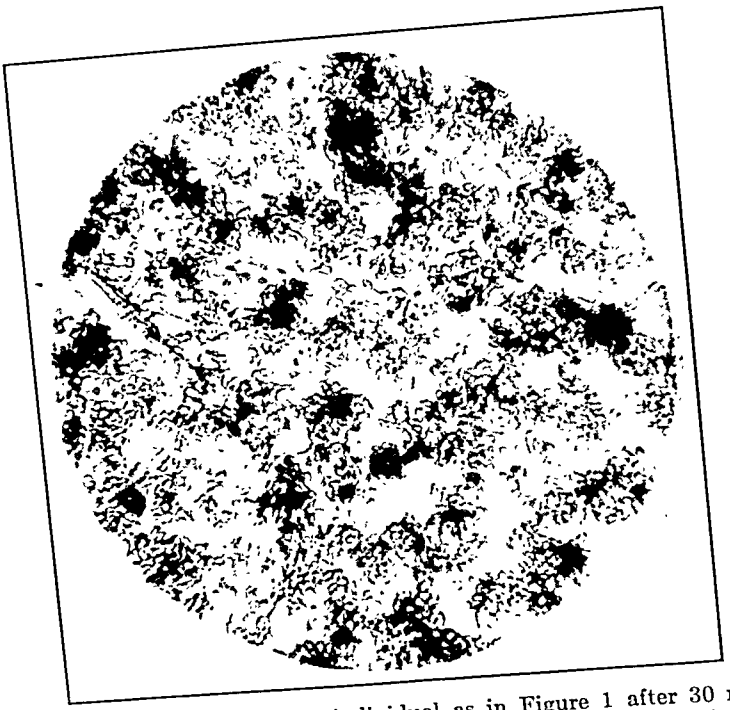


FIG. 2.—Serum and cells of same individual as in Figure 1 after 30 minutes at 5° C. showing how autoagglutination is demonstrated by chilling.

needed in such cases is not another donor, but another patient. Where the auto-test of the patient's serum is negative, but the cross-test positive, an error in blood grouping has probably occurred, or an irregular isoagglutinin is present. In such case, and when the donor's serum clumps the patient's cells, another donor will probably prove suitable.

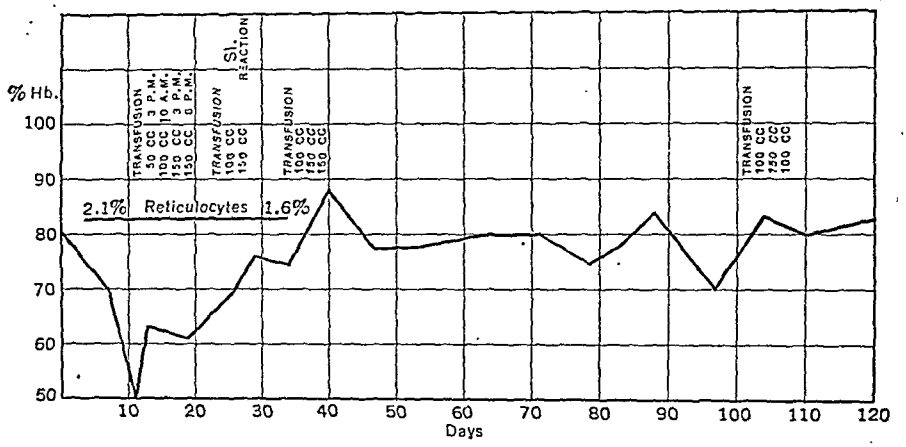


CHART III.—M. L.; aged 16. Acute osteomyelitis of knee (hemolytic Staphylococcus aureus.) Recovery. Strong autohemagglutinin in patient's blood. The first 4 transfusions were given within 30 hours.

The post-transfusion reactions in these 82 cases were characterized by fever of 1 to 2 degrees, or fever and chill, coming on 15 to 30 minutes after the transfusion, and lasting 10 to 15 minutes. Rarely was a reaction delayed as long as 1 hour. This observation is important, as it justifies repeating transfusions with no more than 3 to 4-hour intervals without fear of reactions overlapping. In a few cases, pain in the back and a feeling of constriction about the chest were complained of. In no case were purpura, hematuria, jaundice, or other delayed effects observed. The reactions, however, were severe enough to be very trying, and in weak individuals alarming. Atropin and adrenalin appeared to decrease the severity of the reactions. In this connection the possibility of the so-called citrate reactions is dismissed. Pharmacological studies of the effects of this drug[21] and practical experience,[22,23] to my mind, dispose of this possibility. Moreover, since this series includes 28 transfusions of 400 cc. or more with 2 gm. of citrate in each without any reaction, it is not logical to attribute reactions to citrate when used in smaller amounts.

This study, of course, has definite imperfections, since there are many factors which make it difficult to draw final conclusions. If the sera from a number of patients could be studied with the use of lecithin, by absorption, and by actual titration of the agglutinins, and the effect of transfusion noted on these patients, the relation

of the minor blood agglutinins to post-transfusion reactions would be definitely determined.

Conclusions. The autohemagglutinin (panhemagglutinin) is shown to occur frequently in the blood of patients needing transfusions, and to account for the majority of intra-group incompatibilities.

Evidence is advanced that a large per cent of post-transfusion reactions in carefully performed transfusions may be attributable to this agglutinin.

A technique of blood matching designed to detect autohemagglutinin and suggestions for transfusing in the presence of this agglutinin are given.

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THE EFFECT OF INJECTING CERTAIN ELECTROLYTES INTO THE CISTERNA MAGNA ON THE BLOOD PRESSURE.

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In the course of some observations on factors influencing the blood pressure of dogs we have tested the effect of urine extracts when injected into the cisterna magna. Certain extracts were found to have a marked pressor effect when administered in this way, but this effect was absent or reversed when these extracts in the same dosage were given intravenously. Since the pressor effect of intracisternal injection was not abolished by ashing the extracts and redissolving the residue in water, we were led to surmise that it was dependent on the presence in our extracts of inorganic salts. Accordingly, a study of the action on blood pressure of various electrolytes was undertaken.

Method. Most of the observations were made in dogs; a few goats were studied also. The animals were anesthetized with sodium pentobarbital ("nembutal"), 30 mg. per kg. of body weight, administered intravenously. If during the course of an experiment the animal became restless, small additional doses of the drug were administered. Blood pressure was measured with a mercury manometer connected with a cannula in the femoral artery. The cisterna magna was punctured with a 20-gauge needle connected with a tap which could be opened for removal or injection of solutions, or closed to prevent escape of fluid. Ordinarily, the needle and tap were left *in situ* for the duration of the experiment. In order to minimize changes in intracranial pressure injections were preceded by the removal of an amount of spinal fluid equivalent to the volume of the solution to be injected. When hypertonic solutions were administered, their effects were usually controlled by

the injection of equimolar sodium chlorid. Hypotonic solutions were made approximately isotonic by the addition of sodium chlorid.

In many of the experiments, analyses of the spinal fluid for calcium were made. For this purpose the Clark-Collip[1] modification of the Kramer-Tisdall[2] method was employed.

It was found that whenever respiratory paralysis occurred, a terminal rise in blood pressure, apparently due to asphyxia, was noted. In presenting the data only those effects are considered as significant which lasted for several minutes or longer after the injection; for injections of any liquid, even the dog's own spinal fluid, sometimes caused slight evanescent changes (in either direction) in blood pressure.

With these general methods a series of electrolytes was studied, including sodium, potassium, calcium, magnesium, lead, chlorid, sulphate, nitrate, oxalate, phosphate and citrate ions.

Results. A. Observations on Dogs. *Sodium Chlorid.* In an occasional dog a slight temporary rise in blood pressure might be produced by any intracisternal injection, even that of isotonic salt solution. Such effects were exceptional, lasted only a few seconds, and did not simulate the marked and prolonged effects produced by other ions. Increasing the strength of the sodium chlorid concentration was without effect until concentrations approaching molar were reached. Similar results were obtained with sodium sulphate. These observations indicated that the pressor effects which were obtained with much weaker dilutions of electrolytes cannot be ascribed to osmotic action.

Potassium Chlorid. When solutions ranging between 50 and 100 millimols per liter were injected in doses of 1 cc., a marked difference was observed between the effects of the first and of subsequent injections. The initial injection usually caused a decline in blood pressure. The second injection caused either a decrease —of lesser degree than that produced by the first—an increase, or a diphasic effect, the decline preceding the rise. The third and all subsequent injections usually caused an increase in blood pressure without a preliminary decrease, the effect being more or less proportional to the dose. Different dogs exhibited qualitative similarity but displayed considerable differences in the degree of response (Table 1 and Figs. 1 and 2).

The description applies only to doses within the range mentioned. Smaller amounts usually produced no effects when given initially but, in unusually responsive dogs, caused an increase in blood pressure after the animal had been previously "sensitized" by two or more preceding larger doses. When more concentrated solutions were used the initial injection usually caused a rise in blood pressure which might or might not be preceded by a temporary decline, and subsequent doses produced a marked rise.

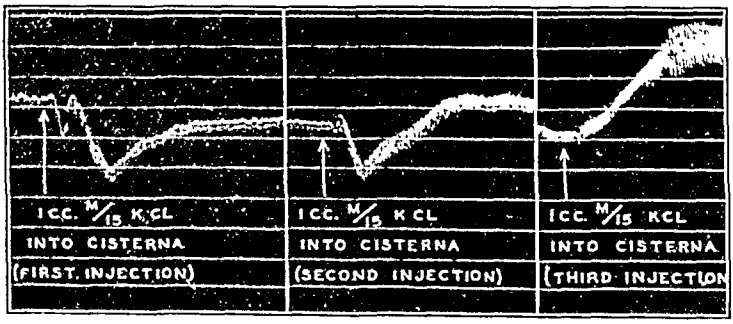
The duration of the pressor response was variable in different

dogs and was usually greater with larger doses. The effect always lasted several minutes and not infrequently persisted for ¼ hour. Fig. 2 illustrates a typical response, which endured for 18 minutes.

TABLE 1.—THE EFFECT ON THE ARTERIAL BLOOD PRESSURE OF DOGS OF THE INTRACISTERNAL INJECTION OF POTASSIUM CHLORID.*

Date, 1935.	Weight of dog, kg.	First injection.		Second injection.		Subsequent injections.	
		Solution injected, millimols per liter.	Change in blood pressure, mm.Hg.	Solution injected, millimols per liter.	Change in blood pressure, mm.Hg.	Solution injected, millimols per liter.	Change in blood pressure, mm.Hg.
Jan. 4	5.0	67	−42	67	+24	50	+18
						50	+20
14	9.0	100	−18	100	+18	50	+ 8
14	8.0	100	+64†	50	+56	33	+ 6
						50	+30
18	10.8	100	−48	100	+20	50	0
						67	+60
22	8.7	100	−18	100	+64	50	+40
23	8.1	100	−16	100	−12	100	+46
						50	+16
24	10.4	67	− 8	67.	+52	50	+20
25	10.0	100	−38	100	+54	50	+34
26	11.5	100	−40	100	+88		
Apr. 5	19.5	67	−28	67	+10		

* The amount of fluid injected was 1 cc. in each instance.
† This increase was preceded by a diminution of 36 mm.

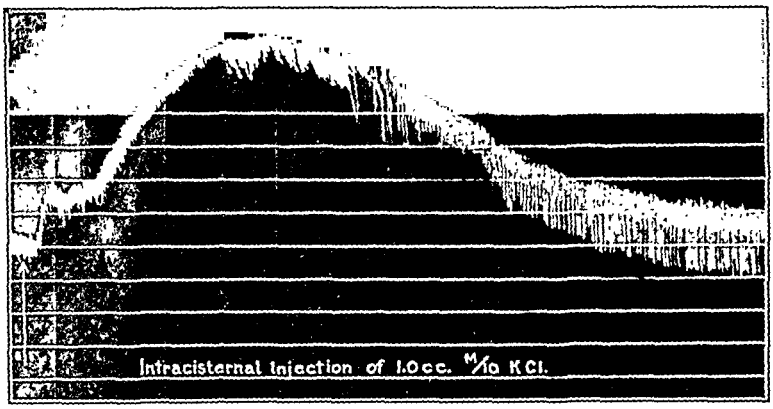


NOTE.—In all figures the curves run from left to right. The time intervals on the base line are 6 seconds. The distance between two adjacent horizontal lines represents 20 mm. of mercury. Arrows denote injections.

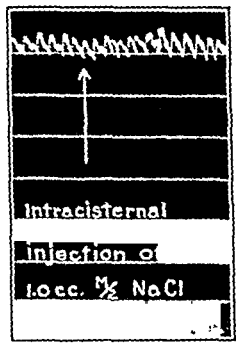
FIG. 1.—The three curves represent typical effects of repeated injections of potassium chlorid, the first injection causing a depressor response, the second producing a diphasic reaction and the third initiating a pressor effect.

Potassium chlorid solutions not only affected the blood pressure but other functions as well. Respiration was usually increased, the breathing often became stertorous, and the respiratory variations in blood pressure became more pronounced (Fig. 1). Sometimes the stimulation of breathing was noted following injections which did not affect the blood pressure. Restlessness, rigidity, opisthotonos

and muscular twitchings were frequently observed; convulsions were noticed only occasionally. The general picture was not unlike that of uremia as observed in patients.



A



B

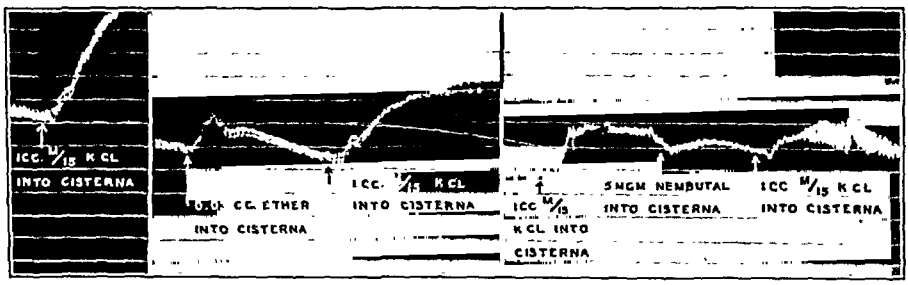
FIG. 2.—The marked pressor effect produced by potassium chlorid (*A*) was not obtained with sodium chlorid (*B*). Since the latter solution was five times as concentrated the records indicate that the pressor response could not have been due to increase in osmotic pressure.

The intravenous injection of equivalent amounts of potassium chlorid had no effect on blood pressure and produced no obvious changes in the general state or in the breathing of the animals. It is, however, of interest to note that Harrison, Friedman and Resnik[3] observed respiratory stimulation following the intravenous administration of much larger amounts of potassium chlorid than were employed in our intracisternal injections. The same authors also observed an increase in the blood pressure in many of their experiments.

To eliminate the possibility that the pressor responses were dependent on the anesthetic employed, a few observations were made on dogs anesthetized with ether. Injections of potassium chlorid produced in them also a well-marked rise in blood pressure.

The pressor effect was sometimes diminished but was not abolished by the previous intracisternal injection of small amounts of ether or of sodium pentobarbital (Fig. 3). The anesthetic did not augment the pressor response. It, therefore, seems unlikely that the effects observed can be ascribed to the narcotics used. Quite possibly the anesthetics, which themselves lower blood pressure when given intracisternally, may tend to make the animal less responsive to the potassium chlorid.

It has seemed desirable to determine, if possible, the location of the area through which the potassium chlorid exerts its effect. The existence of a "vasomotor center" in the floor of the fourth ventricle has long been assumed, but its exact location is unknown.[4,5,6] Furthermore, the recent demonstrations of various vegetative centers in the hypothalamus[7,8,9] have suggested the possibility that the vasomotor effects of medullary lesions might be the result of injury to projection pathways from the hypothalamus rather than to a specific nuclear "center" in the medulla.



A B C

FIG. 3.—Following the injection of ether the pressor response (*B*) to potassium chlorid was somewhat less than before (*A*). The record (*C*) is from another dog and shows that nembutal diminishes slightly the pressor response to potassium chlorid.

In each of 4 dogs anesthetized with sodium barbital, the following experiment was performed. The medulla and cerebellum were exposed by wide removal of the occipital bone and arch of the atlas, and opening the dura. The arachnoid over the outlet of the fourth ventricle was incised. An opening was made in the bone and dura over the left occipital lobe sufficiently large to allow anterior retraction of the occipital lobe, exposing the tentorium. A small ureteral catheter connected with a tuberculin syringe was inserted into the fourth ventricle, after careful removal of any free cerebrospinal fluid with a small pledget of cotton. Through the catheter 0.1 cc. of a solution of potassium chlorid (100 to 1000 millimolar) was injected. A prompt rise in blood pressure occurred in all experiments (Fig. 4*A*). Equal amounts of the solution were then placed upon the dorsal surface of the medulla (below the fourth ventricle) and subsequently upon the upper cervical cord. In no

instance was any effect upon blood pressure demonstrated following these procedures.

The occipital lobe was then elevated from the tentorium and the upper brain stem rapidly severed at the level (intercollicular) of the tentorium. Hemorrhage was controlled by a large moist cotton pack. As soon as the blood pressure reached a constant level (usually 15 to 25 mm. below the previous level), the injection into the fourth ventricle was repeated. In all experiments, a prompt rise in blood pressure occurred. This rise was similar in degree to that occurring previous to the section of the brain stem in 2 experiments (Fig. 4*B*) and was slightly less than that previously observed in the other instances. In 2 experiments, the medulla was then sectioned below the fourth ventricle and the injection immediately repeated. Pressor responses did not occur. Necropsy revealed

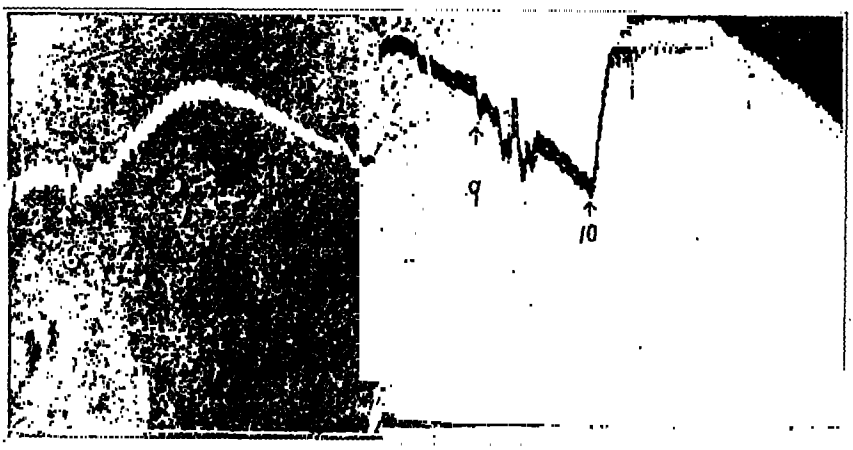


FIG. 4.—Section of the brain stem at the level of the tentorium (9) did not abolish the pressor response to potassium chlorid. (See text.)

complete intercollicular section in 3 of the 4 experiments. In the remaining one a small strand of the superior, lateral portion of the cerebral peduncle remained intact.

These experiments show that the site of action of the injected solution was between the inferior colliculus and the outlet of the fourth ventricle, and that the effect was mediated through pathways extending down the spinal cord rather than through the cranial autonomic efferent channels. On account of the rapidity of occurrence of the effect and the small volume of solution injected, it seems probable that this area lies close to the surface in the floor of the fourth ventricle.

Further studies concerning the more exact localization of the mechanism are in progress.

Calcium Salts. In view of the physiological antagonism[10] between potassium and calcium, it seemed desirable to investigate the

effects of intracisternal injections of calcium salts. Table 2 shows the results of such injections. The calcium salts injected were the chlorid, lactate and gluconate. These salts usually caused a slight decline in blood pressure, but marked diminution was not observed and in some instances no decrease occurred. A significant rise in blood pressure was not produced by calcium salts in any of the experiments.

TABLE 2.—THE EFFECT OF THE INTRACISTERNAL ADMINISTRATION OF CALCIUM SALTS IN THE ARTERIAL BLOOD PRESSURE OF DOGS.

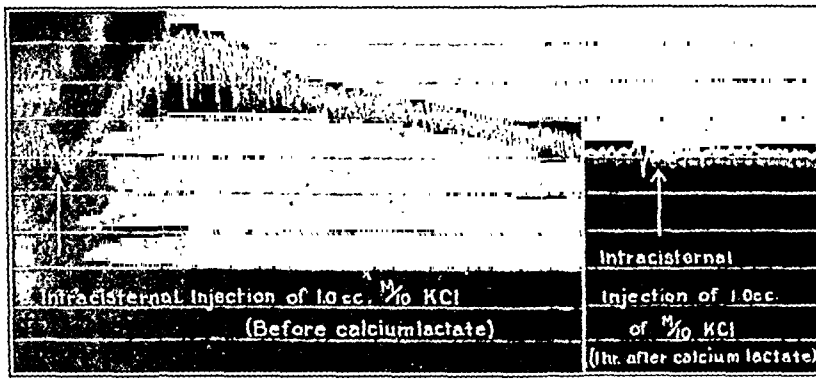
Date, 1934 to 1935.	Weight of dog, kg.	Calcium salt employed.*	Concentration of injected solution, millimols per liter.	Change in blood pressure, mm.Hg.
Dec. 7	14.6	Chlorid	50	− 5
		Chlorid	50	−10
20	10.3	Chlorid	100	−30
22	12.2	Chlorid	50	+ 5
28	6.0	Chlorid	5	−20
Jan. 5	10.5	Chlorid	5	− 5
Feb. 15	12.0	Chlorid	100	−20
		Lactate	(Suspension)	−10
21	10.2	Lactate	118	−10
23	11.3	Gluconate	100	−22
25	8.7	Lactate	50	0
26	8.0	Chlorid	50	− 5
		Lactate	50	− 8
		Gluconate	50	−15
27	8.1	Gluconate	50	−20
		Lactate	100	0
		Gluconate	50	−28
		Lactate	50	−10
28	12.1	Lactate	50	+ 5
		Gluconate	100	0
		Lactate	50	−15
Mar. 1	10.2	Gluconate	50	− 5
		Lactate	50	+ 5
		Gluconate	50	+10

* The amount of solution injected was 1 cc. in each instance.

In contrast to their relatively slight effects on blood pressure, calcium salts were found to have a striking inhibitory action on the pressor effect of subsequently injected potassium chlorid. Doses of the latter which regularly caused marked rise in blood pressure were entirely without effect when administered after calcium salts (Fig. 5). Even so small a dose as 1 cc. of two-hundredth molar calcium chlorid occasionally prevented the rise in blood pressure which otherwise would have followed injection of a much more concentrated solution of potassium chlorid (Fig. 6).

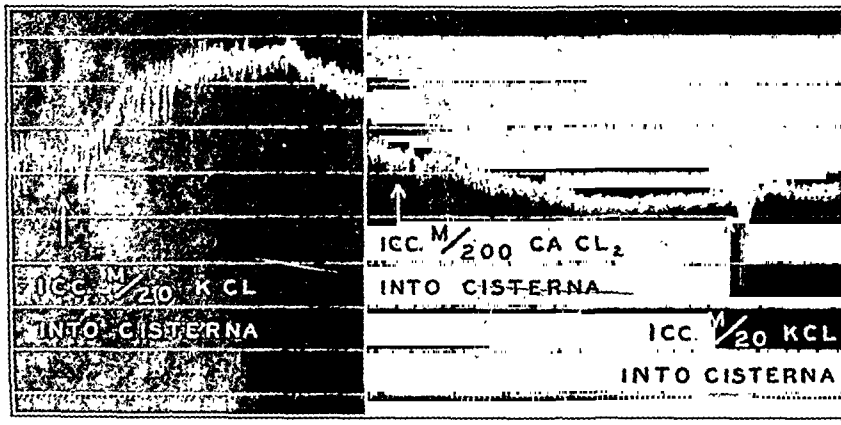
The duration of this inhibitory action of calcium salts varied in different dogs. A comparison (Table 3) of the three different salts seemed to indicate that when they were injected in equimolar amounts the gluconate had the most prolonged effect and the chlorid the least, the lactate being intermediate. A point which seemed of especial interest, and which is illustrated in Table 3, was

the lack of parallelism between the height of the spinal fluid calcium and the effectiveness of the calcium salt in preventing the rise of blood pressure produced by potassium injections. Thus, in several instances the effect of calcium salts in making the animal insensitive to potassium chlorid persisted after the calcium content of the cerebrospinal fluid had returned to a normal level. In other observations the animal recovered sensitivity at a time when the cerebro-



A B

FIG. 5.—The pressor response to potassium chlorid (*A*) was abolished by calcium lactate (*B*.)



A B

FIG. 6.—The very dilute solution of calcium chlorid (*B*) which caused relatively slight decline in blood pressure abolished the pressor response to potassium chlorid (*A*.)

spinal fluid calcium was still considerably elevated. These observations suggested that the calcium content of the nerve tissue rather than that of the cerebrospinal fluid is of chief importance in the inhibitory effect produced by this ion.

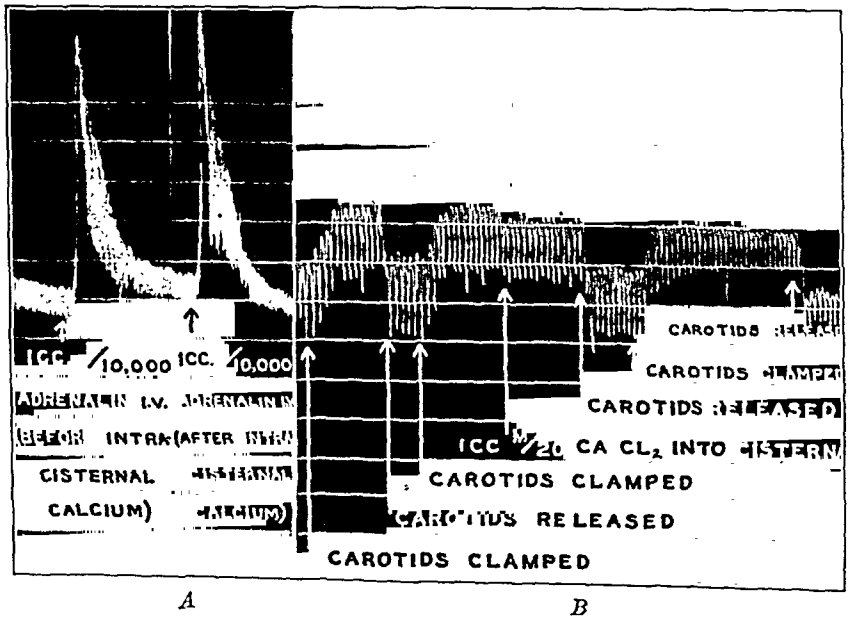
Observations were made in order to determine whether the intracisternal administration of calcium salts would have a general effect in abolishing or in diminishing pressor reactions which were

TABLE 3.—THE RELATION OF THE DURATION OF THE INHIBITORY EFFECT OF CALCIUM TO THE CALCIUM CONTENT OF THE CEREBROSPINAL FLUID.

Date, 1935.	Weight of dog, kg.	Calcium salt injected.*	Concentration of calcium salt, millimols per liter.	Duration of inhibitory effect, hours.	Spinal fluid calcium.		
					Before calcium injection.*	After calcium.	
						At end of period of inhibition.†	At time of recovery of sensitivity.
Feb. 15	12.0	Chlorid	100	2.6	3.2	11.9	9.5
		Lactate	250 (Suspension)	5.5	7.2	5.7	
21	10.2	Lactate	117	4.0	5.2	7.1	
23	11.3	Gluconate	100	4.0	5.1	9.0	4.3
25	8.7	Lactate	50	6.0	4.8	6.4	6.4
		Chlorid	50	3.1	9.0	5.1	5.3
26	8.0	Chlorid	50	2.0	4.2	8.3	6.1
		Lactate	50	3.0	5.4	9.8	7.3
		Gluconate	50	5.0+	5.7	7.0	
27	8.1	Gluconate	50	2.5	5.1	11.0	8.3
		Lactate	50	2.0	6.5	10.5	7.4
		Gluconate	50	1.1	6.4	52.9	8.8
		Lactate	50	0.5	5.7	51.4	5.2
28	12.1	Lactate	50	2.0	4.9	5.1	3.5
		Gluconate	50	3.0	5.4	5.2	4.8
		Lactate	50	2.0	4.7	8.9	3.8
Mar. 1	10.2	Gluconate	50	3.0	5.0	11.5	7.9
		Lactate	50	2.0	5.0	7.1	7.3

* The dose injected was 1 cc. in each instance.

† At the time when these samples were withdrawn the animals were still insensitive to potassium injections. The values in the next column are for samples taken when the animals had recovered sensitivity to potassium injections.



A *B*

FIG. 7.—The injection of calcium intracisternally did not change the response to adrenalin (Fig. 7*A*) or to clamping the carotids (Fig. 7*B*).

not due to central chemical stimuli. As is illustrated in Fig. 7*A*, the response to adrenalin was not altered by the administration of calcium into the cisterna. Similar negative results were obtained as regards the carotid sinus reflex (Fig. 7*B*). The degree of rise in blood pressure produced by clamping the carotid arteries was not altered by calcium injections. It appears, therefore, that the inhibitory action of calcium on pressor agents does not include those which increase the blood pressure through reflex mechanisms or through action on the peripheral vessels.

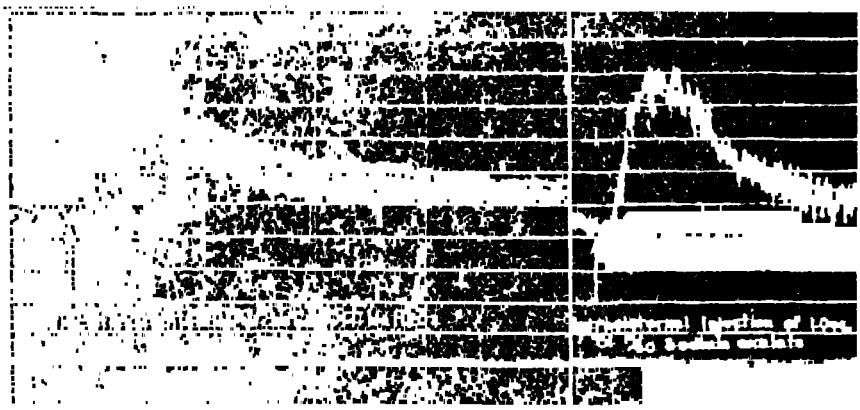


FIG. 8.—Disodium phosphate and sodium oxalate caused pronounced increase in blood pressure.

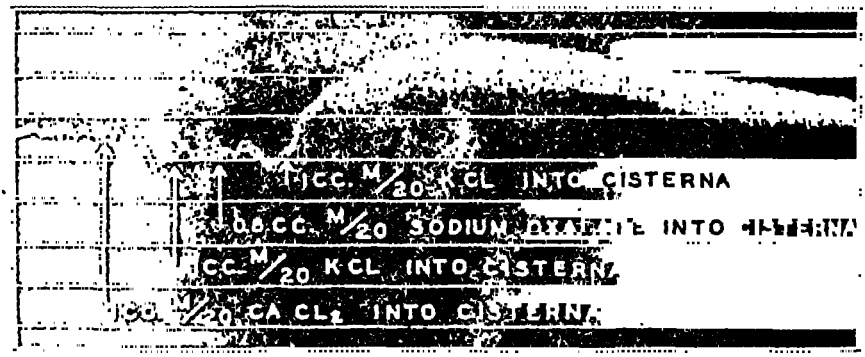


FIG. 9.—Following the injection of calcium chlorid no pressor response was obtained from potassium chlorid. This inhibitory effect of calcium chlorid was removed by the injection of sodium oxalate, the animal now reacting with a marked rise in blood pressure when potassium chlorid was again injected.

The Effect of Anions. No significant effects on blood pressure were noticed after the injection of 1 cc. of the sodium salts of chlorid, sulphate and nitrate in concentrations up to 200 millimols per liter. With larger doses slight increases in blood pressure—apparently due to osmotic effects—were observed. Pronounced rise in blood pressure occurred following the intracisternal administration of di-sodium phosphate, sodium oxalate and sodium citrate

(Fig. 8). These effects could be prevented by the previous administration of calcium salts. Furthermore, administration of these anions abolished the inhibitory effect of calcium salts on the pressor response to potassium chlorid (Fig. 9).

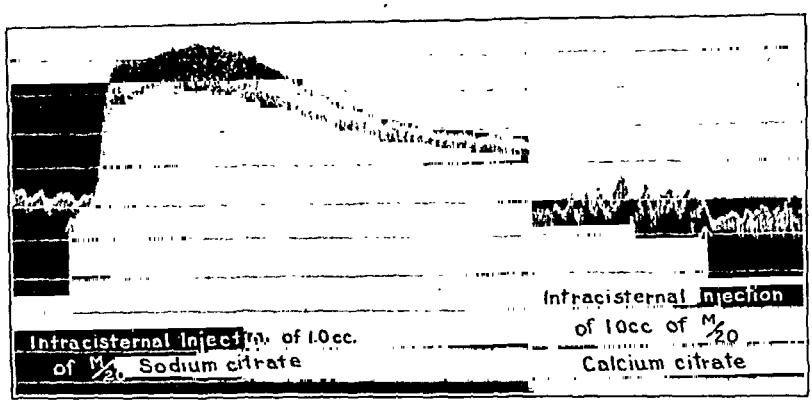


FIG. 10.—The negative result from calcium citrate appears to indicate that the positive response to sodium citrate was due to the calcium binding property of the citrate ion.

The injection of sodium phosphate and sodium oxalate, as expected, was found to cause a marked decrease in the total soluble spinal fluid calcium content. However, the injection of sodium citrate caused a significant decrease in the spinal fluid calcium content in only 1 of 5 observations (Table 4). It is known that citrate

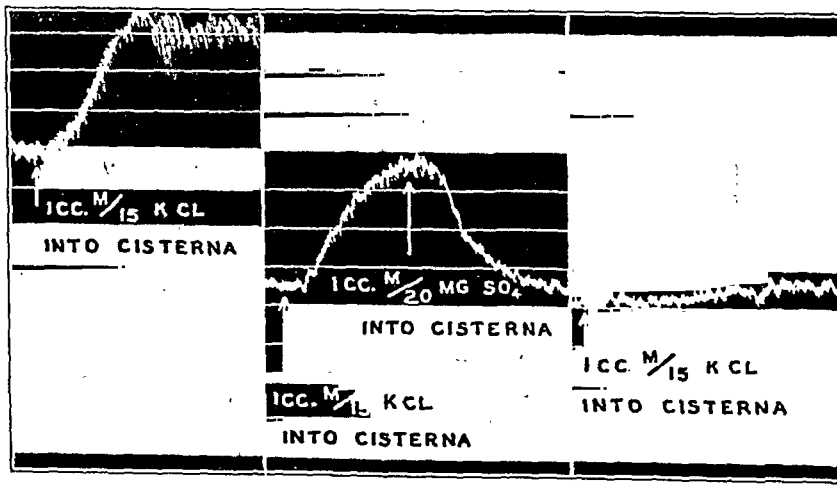


FIG. 11.—When given at the height of a pressor effect produced by potassium chlorid, magnesium sulphate was followed by a decline in blood pressure. A subsequent injection of potassium chlorid was now ineffective.

binds calcium as an un-ionized complex. This fact coupled with the observation that the injection of calcium citrate had no effect (Fig. 10) seems to indicate that the effect of calcium chlorid and lactate is independent of the total concentration and is related only

to the ionized calcium. Since there is evidence which suggests that the choroid plexus is relatively impermeable to calcium salts,[11,12] the rise in spinal fluid calcium, which occurred in certain instances,

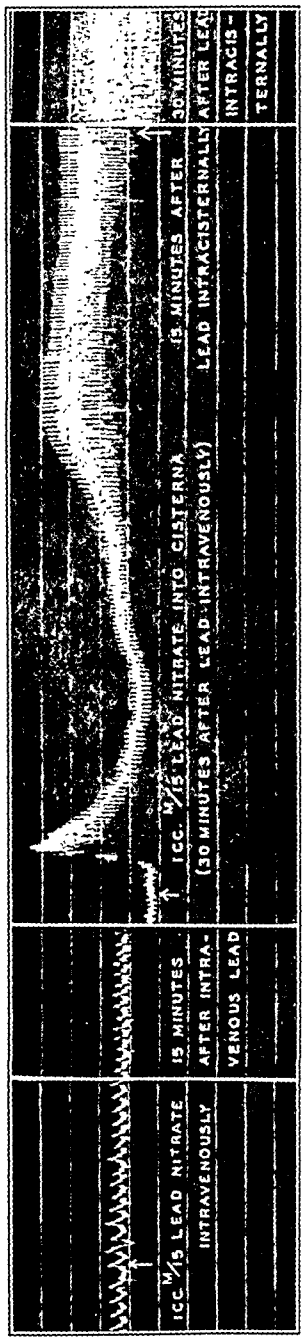


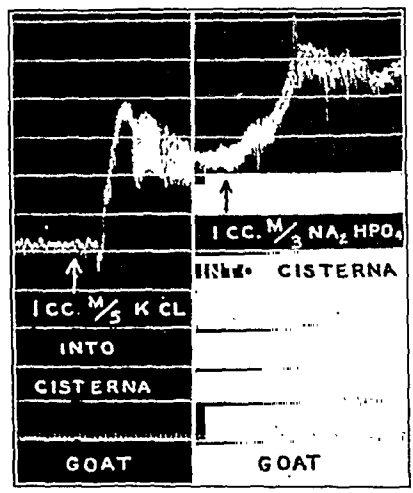
FIG. 12.—In the dose used lead had no effect when administered intravenously. Following intracisternal injection there was an immediate but temporary rise in blood pressure. A few minutes later a prolonged pressor response developed which endured for 30 minutes.

following the injection of citrate can best be explained by the assumption that calcium diffused out of the tissues of the nervous system into the cerebrospinal fluid.

TABLE 4.—THE EFFECT OF SODIUM CITRATE ON SPINAL FLUID CALCIUM.

Date, 1935.	Before.	After.	Amount of sodium citrate.
Feb. 5 . . .	3.8	5.0	1 cc. M/20 sodium citrate.
	4.6	7.1	20 min. after 1 cc. sodium citrate.
6 . . .	5.8	5.4	About 2 min. after 1 cc. M/30 sodium citrate.
		5.7	About 10 min. after 1 cc. M/30 sodium citrate.
Apr. 15 . . .	4.7	3.7	1 cc. M/50 sodium citrate.
	4.0	4.2	1 cc. M/50 sodium citrate.

Magnesium Salts. Only a few observations have been made using the chlorid and the sulphate ions. Insofar as the experiments go, they indicate that these salts have an action similar to, but less pronounced than that of calcium salts (Fig. 11). Doses which in themselves had little or no effect on blood pressure produced a pronounced inhibition of the pressor effect of potassium salts. The duration of this inhibitory action appeared to be shorter than when calcium salts were used. With large doses of magnesium chlorid or sulphate, respiratory paralysis and terminal rise in blood pressure, apparently due to asphyxia, occurred. When magnesium salts were administered at the height of the pressor effect produced by potassium, the blood pressure fell rapidly to a normal level in some observations but not in others.



A *B*

FIG. 13.—The two curves represent two different goats. Potassium chlorid (*A*) and disodium phosphate (*B*) caused well-marked rise in blood pressure.

Lead. In view of the clinical evidence[13] which points toward a relationship between plumbism and increased blood pressure, observations were made concerning the effect of lead nitrate when administered into the cisterna. Single large doses of lead nitrate produced a marked and sustained rise in arterial pressure. When smaller amounts were used a decline in blood pressure from the first injection was obtained, followed by an increase after subsequent doses. The pressor effects of small doses are slower in onset

and more prolonged than those produced by potassium chlorid. Doses of lead nitrate which are without effect when injected intravenously may cause a marked rise in blood pressure when given into the cisterna. These observations are illustrated in Fig. 12.

B. Observations on Goats. In order to determine whether the effects observed in dogs were due to some species peculiarity, it seemed desirable to make observations on other animals. Goats were chosen because they were of a convenient size and further because they represented a species of mammal far removed from the dog.

Goats proved less satisfactory than dogs as experimental animals because they were less readily anesthetized with sodium pentobarbital, and doses sufficient to keep them quiet were likely to be fatal. In two observations not complicated by this difficulty, the qualitative responses were similar to those found in dogs. Fig. 13 illustrates the effects of potassium chlorid and of sodium phosphate.

Discussion. The foregoing results, which are similar in a general way to those obtained by Hastings[18] in a study of the mechanism of tetany, indicate that the arterial blood pressure may be markedly influenced by changes in the electrolyte pattern of the cerebrospinal fluid, and that the effects may be exerted through a nerve mechanism situated in or near the floor of the fourth ventricle.

The most pronounced changes in blood pressure have been obtained by alterations in the amounts of potassium or calcium. It is well known[14,15] that these cations have marked influence on cell permeability, but whether any relationship exists between this action and their effects on blood pressure is uncertain.

Kylin[16] suggested that the increased peripheral resistance of patients with hypertension is the result of disturbance in the sympathetic nervous system secondary to changes in the K/Ca ratio. Weinstein and Weiss,[17] who reviewed the literature on this subject and reported a large series of cases, concluded that the available evidence does not favor this assumption. Calculations from our experiments indicate that the potassium content of the spinal fluid would have to increase by 50 to 100% to produce a marked elevation of blood pressure. (Of course, there is the possibility that man is more sensitive than the anesthetized dog to changes in the concentration of potassium.) More must be known about the amount and state of potassium in nerve cells before a justifiable claim can be made concerning a possible rôle of potassium salts in the production of hypertension.

Of the several anions which cause an increase in blood pressure when injected into the cisterna, phosphate is the only one which is known to accumulate in the body in pathologic states. The recent work of Hastings[18] and of McLean and Leiter[19] have supported the idea that the muscular twitchings of uremia are dependent on a diminution in the amount of ionized calcium in the body fluids, as the result of phosphate retention. Possibly the additional

increase in blood pressure which often occurs in the uremic state is related to the same mechanism, but further evidence is needed before this point can be regarded as established.

The frequency of hypertension in persons exposed to lead has been emphasized by Pal[20] and by Riegel.[21] The experiments of Tscherkess,[22] who showed that lead caused contraction in isolated vessels, pointed toward a peripheral action of this metal. However, our experiments showed that doses which are ineffective intravenously may cause a pronounced elevation when given intracisternally. It seems likely, therefore, that lead hypertension may be due to the deposition of the metal in the nervous system. In favor of this point of view is the fact that lead encephalopathy is accompanied by increase in blood pressure, as Fishberg[13] has emphasized.

Summary. The intracisternal administration of potassium chlorid caused a marked rise in the blood pressure of dogs. Similar doses of sodium chlorid were without effect. Calcium salts produced only slight decline in blood pressure but had a marked and prolonged effect in preventing a rise in blood pressure from subsequent injections of potassium chlorid. Salts such as oxalate, phosphate and citrate, which diminish the ionization of calcium, had marked pressor effects. Salts of magnesium had an action similar to, but less marked than that of calcium salts. Lead caused a delayed but prolonged rise in blood pressure. All of these actions were observed following the intracisternal injection of doses which were ineffective when administered intravenously.

The site of action of these electrolytes appeared to lie in or near the floor of the fourth ventricle. Effects persisted after section of the brain stem above this level, were not obtained after section below, and were elicited by the application of as little as 0.1 cc. directly to this area.

Goats reacted similarly to dogs but seemed to be less sensitive to the various electrolytes.

Since the inhibitory effect of calcium on subsequently injected potassium did not parallel the concentration of calcium in the cerebrospinal fluid, it is believed that the diffusion of calcium into the nerve cells was responsible for its effects.

Since the injection of calcium citrate was ineffective and since the administration of sodium citrate, although sometimes causing an increase in the total calcium content of the spinal fluid, had an effect similar to that from oxalate and phosphate, it is concluded that only the ionized calcium is of importance in inhibiting the blood pressure response to pressor electrolytes.

All of these electrolytes, if given in large doses, produced death by respiratory paralysis. Marked initial stimulation of breathing was produced by potassium, phosphate, oxalate and citrate, but not by calcium and magnesium. The former salts also caused general restlessness and muscular twitchings. These effects were relieved by ionized calcium salts.

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BLOOD TRANSFUSION IN TYPHOID FEVER.

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In our first paper[3] on this subject we reported favorable results in 10 severe cases of typhoid fever treated with blood transfusion. Since that time, we have continued using blood transfusion as a

treatment of severe cases of typhoid fever showing symptoms of marked toxemia. Our present series included only unmistakable cases of typhoid fever verified by blood culture. Our controls were also positive in blood culture and they were given the regular symptomatic treatment only. Our transfused cases and controls were taken from the same group of patients, in such a way that each group represented as far as possible the same severity of the disease in the same period of time, matched individually as closely as possible. Alternative controls could not be made because we could not obtain serial cases of the same severity in the same period of the disease and available at the same time; but we made it a point to select our patients from the severe cases as indicated not only by the clinical symptoms, but also by positive blood culture in every instance. In another report[4] the writers have had occasion to present the prognostic value of blood cultures in this disease and it is because of this fact that we have persisted in making blood culture tests in all of our cases.

Procedure. We remove 150 cc. of blood from the patient and immediately replace them by direct transfusion of 200 cc. of blood from a donor. We purposely started the blood exchange with small amounts, so that we could repeat the treatment as frequently as warranted by the circumstances. If no favorable reactions were observed, or if marked toxemia returned, we repeated the blood exchange *the day following or as often and as many times as required by the severity of the cases* after an interval of 2 to 4 days. Sometimes, we gave as many as 7 transfusions.

In cases, however, where there was intestinal hemorrhage, we did not remove blood from the patient but proceeded at once to transfuse 200 cc. of blood from the donor. Intestinal hemorrhage in itself is already a natural method of exsanguination, so we believed that no further withdrawal of blood from the patient would be necessary or advisable.

Observations. So far, we have treated 41 severe cases of typhoid fever with blood transfusion and 34 cases without. We have succeeded in reducing the fatality from 47.05% in the cases of our control (without blood transfusion) to 24.39% in our transfused cases (Table 1).

TABLE 1.—FATALITY OF TYPHOID FEVER WITH BLOOD TRANSFUSION (1933–1934).

	Recovered.	Died.	Total.	Fatality rate, per cent.
Transfused	31	10	41	24.39
Non-transfused (control)	18	16	34	47.05

Discussion. The rationale of our method of treatment is based on the principle of detoxication brought about by the withdrawal of blood from the patient and its immediate replacement with new blood from a donor. One can easily realize how the removal of the blood of a typhoid patient, loaded with the typhoid toxins and the introduction of new fresh blood from a donor, would bring into the system new protective elements against the disease. We agree with Tremelieres and Tzanck that "blood transfusion is capable of increasing and stimulating the organic defenses already insufficient or

decreased.[5] . . ." Furthermore, it is well known that blood transfusion has always an excellent antihemorrhagic effect.

In some old treatises on internal medicine, we read that many clinicians used to remove blood from their typhoid patients without however giving them a blood transfusion. For instance, Grisolle[2] withdrew from 12 to 16 ounces of blood which, at times, he even repeated twice consecutively; Chirac,[2] 4 to 5 cups every 13 hours until the pulse improved; Forget,[2] 28 ounces; Bouillaud,[2] 3½ pounds, and Louis,[2] 12 ounces to be repeated in severe cases. However, this method of typhoid treatment was later discontinued and fell into disuse for many years. Even in our modern medical literature, we find reports of some clinicians employing simple blood transfusion without partial exsanguination in typhoid fever, particularly in cases with intestinal hemorrhages, but apparently in no case was the treatment followed up sufficiently to make of it one of the more classical therapies of our present days.

For our part, we use partial exsanguination followed at once by blood transfusion as a general treatment in our severe cases of typhoid fever. We believe that this procedure brings about a more rapid detoxication and an early neutralization of the poisons in the system, an immediate introduction of protective elements and the stimulation of the defenses of the body.

The idea of detoxication by partial exsanguination is borne out by clinical observations in typhoid patients with moderate or even severe hemorrhages, after which, convalescence begins in many cases.

The beneficial results of this kind of treatment are readily seen in Table 1. The fatality was actually reduced from 47.05% in non-transfused cases to 24.39% in those that were transfused. As in our previous observations,[4] here again we were able to test the important significance of continued positive blood culture in the appreciation of the ultimate outcome of the case.

After blood transfusion, we have generally observed a decrease in temperature, usually from 2 to 4 days accompanied by a decided improvement of the pulse which becomes stronger and more regular, and a gradual subsidence of other toxic symptoms with a general improved feeling on the part of the patient.

Some cases, however, may develop chills or chilly sensations a quarter or half an hour after the transfusion, lasting for several minutes and followed usually by a momentary rise in temperature which becomes normal or subnormal after a short time, in some cases accompanied by sweating. This temperature soon rises again to about the same level as before the injection but will gradually subside afterwards in favorable cases.

In about half of our series of 41 cases, we have repeated the transfusion of blood as circumstances demanded, as follows:

1 blood transfusion to 22 cases, 2 in 10 cases, 3 in 6 cases, 4 in 1 case, 5 in 1 case, 7 in 1 case.

Treatment by immuno-transfusion is based on the theory that blood which has acquired immunization in typhoid either by actually having had the disease or by vaccinations will be more effective in the treatment of this particular disease. This was true with the observations of Becart,[1] Tremelieres and Tzanck[5] who found good results in the treatment of typhoid fever with immuno-transfusion. But on the other hand, Weil, Rouillard, Netter, Andibert, Tixier and Seze[5] have observed beneficial results with the use of non-immunized blood. We have also begun observations along these lines but until now, we do not feel justified to report them. We have obtained some promising results, but the number of our cases is still too small to warrant definite conclusion.

Summary. This material is presented as a preliminary report; for it is realized that the observations are rather limited and the number of cases (41) included in our series is comparatively small.

Purposely, the author selected only these cases of typhoid fever that were regarded as severe, verified by positive blood culture and with marked toxemic manifestations.

The study was carried as far as possible under similar conditions for the treated and the control cases.

Partial exsanguination has always been practiced immediately preceding blood transfusion, except in those cases where intestinal hemorrhages had occurred.

The fatality percentage was reduced from 47.05% in the control cases to 24.39% in the treated cases.

Conclusion. In spite of the limited number of cases and in view of the promising results obtained, it is thought that this method is of sufficient value that it should be given a fair trial by others in the near future.

The writers desire to express thanks and appreciation to President Jorge Bocobo of the University of the Philippines, and to Dean Fernando Calderon of the College of Medicine, for their generous grants which made these observations possible.

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BOOK REVIEWS AND NOTICES.

FOR AND AGAINST DOCTORS. An Anthology Compiled by ROBERT HUTCHISON and G. M. WAUCHOPE. Pp. 168; illustrated. Baltimore: William Wood & Co., 1935. Price, $2.00.

THIS urbane little anthology pretends to do no more than scratch the surface of the vast corpus of opiniative literature on the virtues and vices of the practitioners of the world's second oldest profession. The material, most of which appeared originally in the *London Hospital Gazette*, is arranged in chronological order, beginning with proverbs of indefinable antiquity and concluding with such irrepressible, if sadly fading, moderns as G. B. S., G. K. Chesterton and Dean Inge, no one of these being very felicitously represented. The dicta come from many lands and many hands, and represent for the most part lay opinion. This ranges widely, as is to be expected, from the grossest abuse to the most unqualified endorsement. The wittiest expressions, as often the most profound, are to be sought in the former category, in accordance with the well-known frailty of human nature. But it is not easy to forget Stephen Paget's words (from the *Confessio Medici*) which conclude this anthology—"If a doctor's life may not be a divine vocation, then no life is a vocation, and nothing is divine."

It is much to be hoped that a more comprehensive collection of similar excerpts may someday be made, and that it may include more of what the doctors have had to say about themselves. It should not include the trivial, however illustrious the oracle, when the literature of all lands is so rich in original and pungent observations on the subject. Meanwhile, this prelude to the potential grand fugue ought to be in the library of every doctor with a sense of humor and a pride in his profession. W. McD., 2D.

DIE LIQUORDIAGNOSTIK IN KLINIK UND PRAXIS. By DR. HANS HEMME, Privatdozent für Neurologie, Chefarzt der neurologischen Abteilung des allgemeinen Krankenhauses Barmbeck in Hamburg. Pp. 205; 96 illustrations. München: J. F. Lehmanns, 1935. Price, Mk. 7.

A CONCISE treatise on the laboratory examination of the cerebrospinal fluid. There are introductory chapters on anatomy and physiology; then follow a description of the technique of the usual tests, and a clear exposition of normal findings. The latter half outlines the characteristics of the cerebrospinal fluid in the chief neurological and neurosurgical disorders. Pathologists, internists, and neurologists will value the book for the accessibility of its material, and for the clear description of the procedures advocated. W. J.

LES PARATHYROIDES. First Fascicle, Volume 2 of Traité d'Endocrinologie. By C. I. PARHON, Professeur à l'Université de Jassy, and M. GOLDSTEIN, Docent à l'Universite de Bucarest. Pp. 524; illustrated. Jassy: H. Goldner, 1935. Fr. francs, 40.

IN this first fascicle of Volume 2 of this treatise, the first that has reached us, the normal and pathological anatomy of the parathyroids, the human and comparative symptomatology of parathyroid disease, their relation to certain disorders of the bones, the skin and the nervous system and to

other endocrine disorders and parathyroid therapy are presented in considerable detail. In the very frequent references to the works of other writers, the volume resembles a monograph more than a textbook; but unfortunately for those wishing to use it as a reference book, the bibliography has been reserved for the second fascicle, which will be on the thymus. One misses an index also, as is customary in books in French; with the method of composition used in this book, an extensive index would have been especially valuable. E. K.

THE CEREBROSPINAL FLUID AND ITS RELATION TO THE BLOOD. A Physiological and Clinical Study. By SOLOMON KATZENELBOGEN, M.D., Associate in Psychiatry, in charge of The Laboratory of Internal Medicine, The Henry Phipps Psychiatric Clinic, The Johns Hopkins Medical School, etc. Pp. 468; 48 tables and 20 charts. Baltimore: The Johns Hopkins Press, 1935. Price, $5.00.

THIS reference book is divided into two parts. The first three chapters deal with the origin of the cerebrospinal fluid, its mode of formation, and circulation. The remainder of the volume is devoted to the chemical constitution of the fluid compared to that of blood.

In a reference work the reader hopes to find each chapter introduced by a statement of the problem followed in turn by a marshalling of data, critical comments and conclusions, and a summary; at the end of the book a complete bibliography and a workable index. Such is the author's plan. Of the components mentioned, only the first leaves something to be desired. Particularly commendable is the scrupulous separation of data from the author's comments. The result is a scholarly and prudent treatise, worthy of a place on the shelf of every researcher in the subject. For the rare gift of an incisive style that points the challenge of the chosen field, the reader of this volume seeks in vain. G. McC.

POLLEN GRAINS. Their Structure, Identification and Significance in Science and Medicine. By R. P. WODEHOUSE, PH.D., Scientific Director of the Hayfever Laboratory, The Arlington Chemical Company, Yonkers, New York. Pp. 574; 123 illustrations and 14 plates. New York: McGraw-Hill Book Company, Inc., 1935. Price, $6.00.

FAR and away the finest text available on the subject of pollen grains from the medical point of view. In Part I, after an interesting historical review, the author discusses methods of collecting pollen in large amounts, preparation of pollen for microscopic examination, atmospheric pollen, hayfever, pollen-grain characteristics. There is a chapter by Professor Gunnar Erdtman of Stockholm on pollen statistics, especially as applied to geologic research. Part II is a key and classification of pollen grains for purposes of identification. The numerous excellent illustrations are for the most part drawings by the authors. All physicians interested in the rôle of pollen grains in the causation of human disease owe Mr. Wodehouse a great debt of gratitude. R. K.

KLINIK UND THERAPIE DER ALLERGISCHEN KRANKHEITEN. By DR. ERICH URBACH, Privatdozent für Dermatologie an der Universtät Wien. 1. Assistant der Universitätsklinik für Geschlechts- und Hautkrankheiten in Wien (Vorstand PROF. DR. W. KERL). Pp. 781; 302 illustrations (26 in colors) and 24 tables. Wien: Wilhelm Maudrich, 1935. Price, Rm. 30.

THE first part of the book is devoted to general and theoretical considerations of the subject, including a detailed discussion of types of hyper- and hyposensitivity, researches in experimental anaphylaxis, the pathogenesis

of allergy, allergens, antibodies, the factors predisposing to allergy, the tissue manifestations of allergy, technique of testing for allergy, preparation of allergens, principles of treatment of allergy. These subjects are well covered and the existing literature is skillfully evaluated.

Part II deals with the special manifestations of allergy, their diagnosis and treatment. Allergy of the respiratory tract (asthma, hay fever, allergic rhinitis) is handled a bit sketchily, although adequately from the standpoint of the general practitioner. Particularly well done are the allergic conditions of the skin, a field in which the author, primarily a dermatologist, has made numerous and valuable contributions. There is appended a very useful table of concentrations of materials to be used in patch testing. Allergists and dermatologists alike will find this volume helpful and worthwhile. R. K.

GLANDULAR PHYSIOLOGY AND THERAPY. A Symposium Prepared under the Auspices of the Council on Pharmacy and Chemistry of the American Medical Association. Pp. 528; 7 charts; 8 illustrations. Chicago: American Medical Association, 1935. Price, $2.50.

THIS physically well made book is the best work of its kind known to the Reviewer. There are 31 chapters by 26 authors, covering the points of major interest in modern endocrine physiology and therapy. With the exceptions of Aschheim and Zondek, all contributors are American or Canadian authors who are recognized authorities on the subject about which they write. Each chapter has a separate bibliography. There is an index. All of the articles have previously appeared in the *Journal of the American Medical Association*. F. D.

CARDIAC OUTPUT AND ARTERIAL HYPERTENSION. By SIDNEY A. GLADSTONE, M.D. Pp. 56; illustrated. New York: By the Author, 1935. Price, $1.00.

THIS 56-page monograph is little more than an elaboration of several papers published recently by the same author. The Grollman Cardiac Output Method has been reinvestigated, is criticized, and a modification developed. This new technique has been employed to estimate cardiac output in a few cases of hypertension. A long theoretical discussion of the causation of hypertension follows. I. S., JR.

DIE THEORETISCHEN GRUNDLAGEN UND MÖGLICHKEITEN DER RÖNTGENDIAGNOSTISCHEN WEICHTEILUNTERSUCHUNG. (Forty-eighth supplementary volume of Fortschritte auf dem Gebiete der Röntgenstrahlen.) By DR. ADOLF ZUPPINGER. Pp. 99; 46 illustrations. Leipzig: Georg Thieme, 1935. Price: Paper, Rm. 16; Bound, Rm. 18.

THIS excellent monograph deals with physical factors that radiologists have empirically come to regard as necessary for high quality films. The subject matter, though technical and replete with formulæ and physical measurements, is admirably presented. While the author does not outline the actual technique for the various Roentgen examinations, he does analyze the importance of the various factors, such as wave length, time of exposure, secondary irradiation, gamma value of films, filtration, screen illumination and the part they play in obtaining excellent roentgenograms. The book contains numerous illustrations and charts which enhance its value. P. H.

INFANT NUTRITION. A Textbook of Infant Feeding for Students and Practitioners of Medicine. By WILLIAMS MCKIM MARRIOTT, B.S., M.D., Professor of Pediatrics, Washington University School of Medicine; Physician in Chief, St. Louis Children's Hospital, St. Louis. Pp. 431; 27 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1935. Price, $4.50.

THIS new edition of Dr. Marriott's book covers in an interesting and yet concise fashion the important aspects of the nutrition of children. A number of changes have been made in this edition, some of which add to its value and some do not appeal to this Reviewer at all. Important advances in our knowledge of the vitamins necessitated complete revision of the appropriate chapter and this has been well done. A new chapter on the relation of allergy to the feeding of children has been added. While perhaps too abbreviated for the man specializing in Pediatrics, it presents adequate information for the cursory reader. Slight revisions throughout the rest of the book have been necessary due to recent progress.

The Reviewer regrets that the publishers did not use the same paper and type as in the previous edition. Most of us read with artificial light and the paper and print of the first edition were kind to eyesight even though some charts were not as clear cut. The author has combined in a greatly condensed form information concerning anhydremia, acidosis and alkalosis occasioned by diarrhea and vomiting in the appropriate chapters on these subjects. True, many of the charts of the old edition were more appropriate to a monograph but the bulk of the chemical information offered a very clear exposition of those subjects to the student or practitioner. The Reviewer regards the new edition as too abbreviated in these matters. The chapters on Rickets, Scurvy and Tetany, while very well written, could be condensed for these topics befit the textbook on Pediatrics better though they should be mentioned in a volume of this type.

Marriott's Infant Nutrition is still the leading small book on this subject for the student. E. T., JR.

CLASSICAL CONTRIBUTIONS TO OBSTETRICS AND GYNECOLOGY. By HERBERT THOMS, M.D., Associate Professor of Obstetrics and Gynecology, Yale University. With a Foreword by HOWARD A. KELLY, Emeritus Professor of Gynecology, Johns Hopkins University. Pp. 265; illustrated. Springfield, Ill.: Charles C Thomas, 1935. Price, $4.00.

ADVANCES in the fields of Obstetrics and Gynecology have been slower than in the sister branches of Medicine and Surgery. Furthermore, obstetricians as a group are not especially known for either their interest in research or for any outstanding interest in the history of their specialty. The present small volume on the history of Obstetrics and Gynecology makes an exception to the above statements. Thoms' contribution is a welcome one to this field of obstetrical textbooks; he has written a valuable book to those interested in obstetrics, and one within the price range of all.

For the first time, we have a small volume in which we can learn something regarding the life and times of past masters in obstetrics; and more especially can read in the original the classical contributions of these authors. Some 60 extracts of two or three pages each are preceded each by a paragraph about the author, while the 7 chapters have appropriate forewords.

Every chapter is interesting. The analysis of the material under appropriate headings such as pregnancy, labor, obstetrical operations, puerperal infection, pelvic deformities, and so forth, is of great assistance to the reader, and each contribution, frequently with a picture of its author, has its fascination for the student of obstetrical history.

The book is well composed: The type is large and clear; a useful bibliography and index are appended. The Reviewer's only complaint is that the author has perhaps been too brief. D. M.

ANATOMY OF THE RAT. By EUNICE CHACE GREENE. Vol. 27 of the Transactions of the American Philosophical Society, held at Philadelphia for Promoting Useful Knowledge. Pp. 370; 338 illustrations, partly in color. Philadelphia: The American Philosophical Society, 1935. Price, $5.00.

IN view of the extensive use of the albino rat for various laboratory purposes it is indeed surprising that there has hitherto not been any book on his normal anatomy more detailed than Hunt's Manual (1924) for students. The present work, somewhat comparable to the good human textbook of Anatomy, obviously therefore supplies a needed want, both for advanced students of Comparative Anatomy and for investigators using the albino rat. After preliminary dissections, thorough dissections were made of each system in at least 10 animals and drawings made by the author of the condition found in the majority. These numerous drawings add greatly to the value of the book. This work in conjunction with the data contained in H. H. Donaldson's "The Rat" (second edition, 1924) places knowledge of the anatomy of this animal far beyond that of any other lower animal and in some respects of man himself. E. K.

THE OBSTETRIC PELVIS. By HERBERT THOMS, M.D., F.A.C.S., Associate Professor of Obstetrics and Gynecology, The School of Medicine, Yale University. Pp. 115; 50 illustrations. Baltimore: The Williams & Wilkins Company, 1935. Price, $2.50.

THIS monograph presents in a collective manner the essence of the author's many published contributions to this subject, together with pertinent comments on those of others. He discusses normal and variant pelves in both their anatomical and clinical relations in a clear and lucid manner. Of specific interest are his observations on pelvimetry: the frequent findings of marked differences in the true or internal measurements as revealed by Roentgen ray, in contrast to what might have been expected from external pelvimetry substantiates his feeling that every primigravida should have roentgen pelvimetry. His technique for pelvic mensuration as well as for fetal cephalometry is given in detail. In an excellent chapter on the early determination of disproportion are his views as to the various factors concerned, and the value of roentgen pelvimetry. The funnel pelvis, the dolichopellic pelvis and the recent classification of the abnormal pelvis by Caldwell and Moloy are thoroughly considered. A valuable bibliography is appended.

This work should be of value both to the obstetrician and to his co-worker the roentgenologist. P. W.

BIBLIOGRAPHY ON BLOOD TRANSFUSION, VOLUME I. (International Bibliography on the Problems of Blood Transfusion and the Theory of Blood Groups, 1900–1933.) By DR. E. KOENIG. Pp. 226. Leningrad: Professor E. Hesse, 1935. Price, 12 p., 50 k.

THIS publication consists of a list of 4423 articles on blood transfusion and blood groups which have appeared in the world literature between 1900 and 1933. The finding of any article in the list is facilitated by classification into subtopics, a system of cross-indexing and an author index. The preface and section titles are written in Russian, German, English, French and Italian. Titles of articles in Russian or languages other than German, English, French or Italian are duplicated in German. Such a work as this is clearly of great value to anyone investigating the literature on blood transfusion. L. L.

NEW BOOKS.

Great Doctors of the Nineteenth Century. By SIR WILLIAM HALE-WHITE, K.B.E., M.D., LL.D. (HON.), F.R.C.P., Consulting Physician to Guy's Hospital. Pp. 325. Baltimore: William Wood & Co., 1935. Price, $5.00.

American Martyrs to Science Through the Roentgen Rays. With a Short Glossary of the Scientific Terms used in the Text. By PERCY BROWN, M.D., F.A.C.P., F.A.C.R., Historian and Former President, American Roentgen Ray Society. Pp. 276; 55 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, $3.50.

Pediatric Nursing. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine; Pediatrician-in-Chief to the St. Mary's Group of Hospitals, etc., assisted by Beryl E. Hamilton, R.N., Graduate of St. Luke's Hospital, St. Louis. Pp. 568; 144 illustrations and 7 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, $3.00.

Cardiac Output and Arterial Hypertension. By SIDNEY A. GLADSTONE, M.D. Pp. 56; illustrated. New York: By the Author, 1935. Price, $1.00. (Review p. 856.)

The Chemistry of Natural Products Related to Phenanthrene. By L. F. FIESER, Associate Professor of Chemistry, Harvard University. Pp. 358. New York: Reinhold Publishing Company, 1936. Price, $6.50.

Tuberculosis. (Vol. 16 of Clio Medica Series). By GERALD B. WEBB, Former President, National Tuberculosis Association; Lecturer on Medical History, University of Colorado; President, Colorado Foundation for Research in Tuberculosis. Pp. 205; 17 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, $2.00.

How to Feed Children in Nursery Schools. By MARY E. SWEENY and DOROTHY CURTS BUCK, Physical Growth Staff, The Merrill-Palmer School. Pp. 84; illustrated. Detroit: The Merrill-Palmer School, 1936. Price, Gratis.

Die Werke des Hippokrates. Herausgegeben von DR. MED. RICHARD KAPFERER unter Mitwirkung von Prof. DR. GEORG STRICKER, Würburg. Book 7 (Price, Rm. 7.50; Pp. 85): Die Natur (Konstitution) des Menschen; Die Nahrung; Die Säfte (The Nature (Constitution) of Man; The Nutriments; the Humors). Book 10 (Price, Rm. 5.25; Pp. 75): Die Krisen; Die Kritischen Tage; Prognostikon (The Crises; The Critical Days; Prognostics). Stuttgart: Hippokrates Verlag G.M.B.H., 1934 and 1936, respectively. (To be published in 25 parts costing *ca.* Rm. 100, card binding.)

Time of Ovulation in Women. A Study of the Fertile Period in the Menstrual Cycle. By CARL G. HARTMAN, Department of Embryology, Carnegie Institution of Washington, Johns Hopkins Medical School, Baltimore, etc. Pp. 226; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, $3.00.

Cancer Commission Committee Studies. The California Medical Association. (The results of a five-year correlated study by one hundred and fifty members of the medical profession). Pp. 123. San Francisco: J. W. Stacey, Inc., 1936. Price, 75c.

Medical Papers. Dedicated to Henry Asbury Christian. Physician and Teacher. From his Present and Past Associates and House Officers at the Peter Bent Brigham Hospital, Boston, Massachusetts. In Honor of his Sixtieth Birthday, February 17, 1936. Edited by ROBERT F. MONROE, Peter Bent Brigham Hospital. Pp. 1000; illustrated. Baltimore, The Waverly Press, 1936. (No price given.)

Medical History of Contraception. By NORMAN E. HIMES, PH.D. Medical Foreword by ROBERT LATOU DICKINSON, M.D., F.A.C.S. Pp. 521; 30 illustrations and 29 tables. Baltimore: The Williams & Wilkins Company, 1936. Price, $7.00.

Protoplasm. By WILLIAM SEIFRIZ, PH.D. (Johns Hopkins University), Professor of Botany, University of Pennsylvania, Philadelphia. Pp. 584; 179 illustrations. New York: McGraw-Hill Book Company, Inc., 1936. Price, $6.00.

Photoimmunization and Photovaccination. By S. PESKIND, B.S., M.D., Cleveland, Ohio. Pp. 13. Cleveland: The S. P. Mount Printing Company, 1936. (No price given.)

The Surgical Clinics of North America, Volume 16, No. 1 (Chicago Number, February, 1936). Pp. 356; 78 illustrations. Philadelphia: W. B. Saunders Company, 1936. Price, Paper, $12; Cloth, $16 (per clinic year February–December, 1936).

Parenteral Therapy. A Ready Reference Manual of Extra-oral Medication for Physicians, Dentists, Pharmacists, Chemists, Biologists, Nurses, Medical Students and Veterinarians. By WALTON FOREST DUTTON, M.D., Formerly Medical Director, Polyclinic and Medico-Chirurgical Hospitals, Graduate School of Medicine, University of Pennsylvania, etc., and GEORGE BURT LAKE, M.D., Formerly Special Lecturer in Hygiene, Purdue University, etc. Pp. 376; 90 illustrations: Springfield, Ill.: Charles C Thomas, 1936. Price, $7.50.

NEW EDITIONS.

Basal Metabolism in Health and Disease. By EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute of Pathology; Professor of Medicine, Cornell University Medical College, New York; Physician-in-Chief to the New York Hospital. *Pp. 494; 99 illustrations, 67 tables.* Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $5.00.

A Guide to Human Parasitology. For Medical Practitioners. By D. B. BLACKLOCK, M.D. (EDIN.), D.P.H. (LOND.); D.T.M. (LIVER.), Professor of Tropical Hygiene, Liverpool School of Tropical Medicine, The University of Liverpool, and formerly Professor of Parasitology; Director of the Sir Alfred Lewis Jones Laboratory, Freetown, Sierra Leone, West Africa, and T. SOUTHWELL, D.Sc., PH.D., A.R.C. Sc., F.Z.S., F.R.S.E., Walter Myers Lecturer in Parasitolbgy, School of Tropical Medicine, The University, Liverpool, etc. Pp. 259; 122 illustrations, 2 colored plates. Second edition. Baltimore: William Wood & Co., 1935. Price, $4.00.

Lectures on Diseases of Children. By ROBERT HUTCHISON, M.D., LL.D., F.R.C.P., Consulting Physician to the London Hospital and to the Hospital for Sick Children, Great Ormond Street. Pp. 452; 106 illustrations. Seventh edition. Baltimore: William Wood & Co., 1936. Price, $6.75.

Roentgenographic Technique. A Manual for Physicians, Students and Technicians. By DARMON ARTELLE RHINEHART, A.M., M.D., F.A.C.R., Professor of Roentgenology and Applied Anatomy, School of Medicine, University of Arkansas; Roentgenologist to St. Vincent's Infirmary, Baptist State, Missouri Pacific, and the Arkansas Children's Hospitals, Little Rock, Arkansas. Pp. 431; 183 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $5.50.

PROGRESS
OF
MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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THE POST-TRAUMATIC PERSONALITY DISORDERS.

THE great interest manifested during the past few years in the problems of mental disorders following head trauma continues unabated among psychiatrists and neurologists here and abroad. From both a scientific and a medico-legal standpoint these problems are assuming an ever increasing importance. Johnson[1] has briefly reviewed the contributions in this field up to 1934 in this journal. The present review will be confined to a consideration of the post-traumatic psychoneuroses and their organic counterpart, the so-called traumatic constitution or traumatic encephalopathy, disregarding the acute traumatic psychoses, post-traumatic mental deterioration, traumatic epilepsy, and the traumatic precipitation and aggravation of other psychiatric and neurologic disorders. These subjects, as well as the one under consideration here, have been discussed fully in a recent publication of Ebaugh and Benjamin.[2]

The differentiation of traumatic encephalopathy from functional disorders following trauma has not only therapeutic but also medico-legal significance, since many courts refuse or grant only reduced compensation to cases of post-traumatic psychoneurosis. The differential diagnosis can be extremely difficult, requiring minute neurologic and psychiatric examinations (Strauss and Savitsky[3] reviewed by Johnson).[1] The problem is further complicated by the frequent simultaneous occurrence of organic and functional post-traumatic manifestations in the same patient. It is therefore not surprising that considerable difference of opinion and perhaps some confusion still exist concerning these conditions. Several publications of the past year have contributed toward a clearer understanding of the issues involved.

Wechsler[4] presents a series of 100 cases of which 27 gave obvious objective evidence of brain injury, whereas the remaining 73 presented no gross signs of organic involvement but complained of subjective disturbances such as headache, dizziness, impairment of memory, fears, anxieties, vasomotor disturbances, tremors, impairment of vision. He places these post-traumatic syndromes in the following 4 classes: (1) Malingering, in which there is a conscious and purposeful feigning of illness in order to avoid responsibility or to derive gain (unalloyed malingering is extremely rare, being found only once in the author's series); malingering with hysteria was present in 2 cases; (2) post-traumatic hysteria, the most common post-traumatic sequela that is unaccompanied by gross organic involvement. Wechsler diagnosed this condition outright in 37 of his cases, in addition found hysteria with traumatic encephalopathy 17 times, and hysteria combined with malingering twice. He emphasizes that the diagnosis should be based on both negative and positive criteria, including under the former a history of either no or very brief unconsciousness, no clinical signs of brain injury, no evidence of fracture, and a negative encephalogram; and under the latter positive evidence of a true hysterical reaction precipitated by trauma in an individual with an underlying neurotic personality. The trauma sets in motion the same mental mechanisms as in any other hysteria and serves as a convenient solution of industrial, social, marital, familial or psychosexual conflicts; (3) concussion or traumatic encephalopathy, found in 11 cases alone, and in 17 cases in combination with hysteria. In every case there was a history of more or less prolonged unconsciousness; minute neurologic signs were found in only a few. Typical for these causes are the history of unconsciousness, the absence of psychogenic causal factors, the persistence and severity of the symptoms, and positive encephalographic findings. The author quotes Martland,[5] Foerster and Penfield,[6] Bielschowsky,[7] Rand and Courville[8] and Friedman[9] as having contributed greatly to the knowledge of the anatomic changes underlying this condition, such as minute hemorrhages, glial changes, cell and fiber degeneration, disturbed cerebrospinal dynamics, ventricular distortion, and brain atrophy; (4) traumatic neurosis, diagnosed in 5 cases. Wechsler calls attention to the fact that this term is frequently used synonymously with traumatic hysteria, but believes that one is here dealing with two distinct entities. Clinically this condition differs little from hysteria, but it is apparently not dependent on the unconscious use of the accident to solve difficulties that have nothing to do with the trauma. One is not dealing with a patient who has a neurotic personality to begin with, but rather with a previously well adjusted individual who, following a serious threat to life, without serious head injury, develops symptoms which are not amenable to suggestion or other forms of psychotherapy. There are no demonstrable cerebral changes, hysterical mechanisms cannot be elicited, and compensation does not play a predominant rôle.

Ebaugh and Benjamin[2] point out that the contributors to this field vary greatly in their use of terms, evaluation of symptoms, and estimation of the frequency and medico-legal disposition of the various conditions to be differentiated. After mentioning the contributions

of Brun,[10] Kardiner,[11] Kennedy,[12] Hall and Mackay,[13] Monakow,[14] Naegeli,[15] Riese,[16] Ritter,[17] Rosenstein,[18] Schaller and Somers,[19] Sperling,[20] Strauss and Savitsky,[3] and Wechsler,[4] they suggest the following classification of the post-traumatic minor personality disorders, which in many respects coincidents with that of Wechsler:

I. Traumatic encephalopathy (traumatic constitution): A, Simple type, with subjective complaints of headache, vertigo, irritability, fatigue, impairment of memory; B, with secondary psychogenic symptoms; C, with malingering.

II. Post-traumatic functional disorders: A, Post-traumatic hysteria (rarely other psychoneuroses): a true hysteria precipitated by trauma in an individual with an underlying neurotic personality; may be accompanied by malingering; B, compensation neurosis: a hysteria in which the wish for compensation plays a leading rôle in the unconscious production of symptoms; may be accompanied by malingering; C, traumatic neurosis or terror neurosis: a neurosis, usually hysteriform with pronounced anxiety features, in which the psychogenic mechanisms differ from those in ordinary hysteria.

III. Malingering.

In their discussion of traumatic encephalopathy the authors emphasize that no physician is justified today in denying the existence of organic factors in post-traumatic cases on the basis of a cursory neurologic examination and the impression that the patient is a "neurotic." Kennedy's[12] anamnesic and clinical criteria are presented (Johnson[1]); they are held to be of great value in giving a general orientation as to the probabilities in any case, but not to be conclusive evidence. The authors, in common with Strauss and Savitsky,[3a] stress the importance of a minute neurologic examination; minimal signs will be found in a great many although by no means all cases. Slight differences in reflexes on the right and left side, diminished vibratory sensation in both lower extremities, diminished corneal reflexes, and difficulty in lateral conjugate gaze are mentioned as but a few of the many findings reported. The authors' own experience confirms the opinion of Foerster,[21] Foerster and Penfield,[6] Friedman,[9] and many others that encephalography is a highly valuable adjunct to clinical investigation in this field. They emphasize further the great importance of a detailed formal psychiatric examination, particularly of the sensorium. Special tests for apperception, retention and recall, memory, and organic fatigability are recommended. The Rorschach test is mentioned as being of great value in cases where the differential diagnosis between encephalopathy and the functional syndromes is particularly difficult, and reference is made to the work of Oberholzer[22] in this respect.

In their consideration of the functional post-traumatic disorders and malingering, the authors agree fully with Wechsler's[4] definition and delimitation of the latter term, and share his opinion that unalloyed malingering is rare. In discussing the psychoneurotic reactions, they point out that whereas *a priori* it might be expected that any type of neurosis could be precipitated by head injury, empirically almost all of these cases are hysterias, with or without anxiety, and regard this as due to the specific predisposition of the hysterical personality to use all possible situations as a means of escape into illness, as well as to the

abnormal suggestibility of the hysterical personality. They furthermore agree with Wechsler that the diagnosis should not be made merely through the exclusion of organic signs, but requires positive evidence of hysterical mechanisms. They base their differentiation of compensation neurosis from other post-traumatic hysterias not on the grounds of true etiology, which in both cases lies in conflicts which have no relation to the trauma, but rather on the practical grounds that in some patients the compensation motive plays a leading rôle in the production and persistence of symptoms, and that in these cases a lump sum settlement is the best and usually the only therapy. In opposition to Naegeli and others, they do not feel that the compensation neuroses constitute the majority or even a large percentage of post-traumatic functional disorders. In common with Strauss and Savitsky[3b] and Wechsler they reserve the term traumatic neurosis for a specific and infrequent syndrome first described by Horn[23] under the name of *Schreckneurose*, and subsequently discussed by Bernhard,[24] Libman,[25] and Sperling.[20] It is typical that it occurs only following a serious threat to life in such a situation that the patient has time to be aware of and terrorized by the impending disaster; accordingly it is frequent in war and earthquakes, and is seen occasionally in mining catastrophes and sea disasters, but almost never in the ordinary industrial and automobile accidents. Clinically the symptoms are usually those of an anxiety state, with particularly characteristic dreams in which the patient relives the traumatic situation. Unless complicated by secondary hysterical symptoms the condition tends to clear up spontaneously. The psychopathologic mechanisms differ from those in true hysteria, but are not fully understood as yet (Kardiner[11] and Fenichel[26]).

In a recent article Sands[27] classifies these syndromes in an analogous manner, namely as post-traumatic constitution, traumatic neurosis, traumatic hysteria, and malingering, but uses the term traumatic neurosis to apply to individuals who have recovered from a brain injury, frequently of the cerebral concussion type, and who do not show any neurologic or encephalographic signs, and yet show definite personality changes in the form of irritability, brooding, dizziness, and so forth. He reserves the term post-traumatic constitution for cases showing definite neurologic or encephalographic changes. In the same article this author presents an excellent study of brain changes due to head trauma. He finds that the post-traumatic sequelæ are due to loss of brain tissue, meningo-cortical adhesions, cicatricial contraction, collections of fluid in the meninges and interference with proper cerebrospinal fluid and lymphatic circulation. He advances evidence that significant brain injuries may occur without loss of consciousness.

Blau[28] has recently presented an exhaustive survey of post-traumatic behavior disorders in children. The author finds, in agreement with Strecker and Ebaugh[29] and Kasanin,[30] a marked similarity between these conditions and the postencephalitic behavior disorders. Typical are overactivity, restlessness, destructiveness, impulsiveness, assaultiveness, cruelty to animals, emotional instability, temper tantrums, truancy and delinquency. The prognosis in most cases was poor. The formal intellectual faculties were relatively well retained.

The therapy of the conditions under consideration requires little special mention. All contributors are agreed that the majority of post-traumatic psychoneuroses should be treated by exactly the same methods as in the usual non-traumatic cases. Compensation neuroses are always benefited by a lump sum settlement. The traumatic or terror neuroses tend to clear up spontaneously. The treatment of traumatic encephalopathy must be primarily palliative. Penfield[31] has relieved post-traumatic headaches through encephalography.

The possibilities of the prevention of post-traumatic psychoneuroses has aroused interest in recent years. Dershimer[32] comments on the work at the Fisher Body Company at Cleveland, where practically no psychoneurotic states have developed following the employment of a psychiatrist. The principal method of prevention is through the dissemination of knowledge concerning the causes of the psychoneuroses to employers and employees. FRANKLIN G. EBAUGH, M.D.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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PROGRESS IN RHINOLOGIC ASPECTS OF ALLERGIC DISEASE WITH ESPECIAL REFERENCE TO IONIZATION.

THERE has been a continuous and increasing appreciation of the rôle of allergy in the production and maintenance of otolaryngologic disease. This is reflected not only in the literature of the specialty but also in the diminishing attack upon the interior of the nose and paranasal sinuses. The incidence of allergy in otolaryngologic practice is higher than what is usually believed. Baum[1] reviewed a series of 2000 patients and found some 700 with nasal difficulty, 191 (27%) of which were allergic. Thus practically 1 out of every 4 patients in the otolaryngologists' office that has chronic nasal difficulty is allergic. Furthermore, if one considers the ratio of these allergic cases to the total number of patients studied (2000) one finds that 9.5% of all patients with a chronic complaint that seek aid of the otolaryngologist, or about 1 in every 10, are definitely allergic. A similar review of 1000 cases by Hansel[2] disclosed 142 cases of allergic disease in 324 patients with nasal disorder. Here about 40% or 2 in every 5 cases of nasal disease, are allergic and about 14% or 1 in every 7 patients routinely seen in practice, exhibits allergic phenomena. Undoubtedly if one considered acute illnesses, the percentages would be definitely reduced, but still of major importance. Kuhn, in a discussion of Vaughn's[3] paper, reported similar figures. It is obvious that the high incidence of allergic disease in routine otolaryngologic practice should be borne in mind, and this disorder must be considered whenever confronted by nasal symptomatology.

There have appeared a fair number of contributions[4–9] dealing with the general subject of nasal allergy and having as their main theme the frequency that allergy is encountered; the importance of considering it as a possibility in the differential diagnosis of nasal disease; the marked aid in diagnosis that is afforded by cytologic examination of the secretion; and the importance of proper diagnosis of the etiologic allergic factor. Many, further, dwell upon the futility of intranasal surgery except as a means of promoting drainage in secondary suppuration or relieving nasal obstruction. Watkins[5] especially calls attention to the fact that even multiple surgical operations frequently fail to give relief in allergic individuals except when infection with retention

is present as a complicating factor, and points to the frequent disappearance of polypi after proper allergic therapy.

As an aid in differentiating infectious from allergic nasal and paranasal sinus disease, the work of Buhrmester[10] must receive consideration. He found that in allergic disease the nasal secretions had a higher water content, averaging about 97% as compared to 90% found in infectious disease. As a consequence the total solids were 3% in allergic disease and 10% in infectious disease. There is present about three times as much total solids in infectious exudate as there is in allergic secretion. The protein content varied from 0.21% to 3.82% in allergic secretions as compared to the 3.45% to 16.23% found in infectious exudates. Similar figures have been reported by Mittermaier.[11] The ash in the total solids was much higher in the allergic secretions than in infectious exudate. The calcium was higher in infectious disease as compared to allergic disease averaging 11% and 9% respectively. The allergic secretions were found to have a higher pH or become more alkalin than the infectious exudates.

As an aid to the diagnosis of allergic disease, an intramucosal test similar to intradermal tests was described by Dean, Linton and Linton.[12] Appropriate extracts were either injected or applied to scratches made in the mucous membrane of the anterior end of the inferior turbinal. A positive reaction consisting of swelling, edema or even a wheal, would appear within 30 minutes, although a delayed reaction was also noted. In some instances, a positive intranasal mucosal reaction was obtained when the dermal test was negative.

Non-specific methods of treating nasal allergy continue to receive attention. Palmer[13] describes the effect of treating the nasal mucosa with phenol in 30 cases of nasal allergy and noted definite improvement in 80%. Histologic study of the mucosa after treatment disclosed an increase in the fibrosis with a decrease in the vascularity and edema of the tissue. Bernheimer[14] reported on the final results in 40 patients treated 3 years prior by Cutler and himself by the use of radium placed within the nose. He found 47% symptom-free, 22% had some sneezing, but no obstruction or rhinorrhea, 8% moderately comfortable, and 23% with little or no relief. There was no success in similar treatment of 12 patients afflicted with seasonal hay fever. By far the most important contribution to the literature dealt with the subject of ionization in the treatment of allergic disease. There were many contributions on the subject, dealing not only with the technique, but also with the histologic effects upon the nasal mucosa. Intranasal ionization, more properly called iontophoresis, has been brought to the attention of rhinologists and allergists as a worthwhile means of therapy in those cases in which specific immunization is difficult to effect or undesirable. Iontophoresis consists in the introduction of medical ions into the tissue by means of the galvanic current. It is nothing new, having been utilized over 30 years ago. Drugs or chemicals are forced into tissue by virtue of the fact that an aqueous solution of the drug or chemical contains a number of positively and negatively charged ions arising from the dissociation of the substance when placed into solution. If a constant direct or galvanic current is permitted to flow through the solution, the attraction of unlike charges

will cause the positively charged ions to move and collect at the negative pole and the negatively charged ions to move and collect at the positive pole. For example, a solution of sodium chlorid will have freely disassociated positive sodium ions and negatively charged chlorid ions. Upon being subjected to the galvanic current the sodium ions being positively charged will collect at the negative pole and the chlorid ions at the positive. By taking advantage of the migration of ions, heavy metals such as zinc, tin and cadmium have been utilized in therapeusis. Whether or not heavy metals are actually deposited in the tissues is still open to question. Lierle and Sage,[15] in a study of zinc ionization in the treatment of otorrhea, were unable to demonstrate that the zinc was actually deposited in the tissues of laboratory animals used in their experiment. Wenner,[16] on the other hand, was unable to demonstrate by means of chemical methods that zinc was deposited in the skin and cartilage of the ear of a rabbit. The source of the current utilized in the procedure may be batteries, which give a pure constant current. McFarland[17] described an inexpensive set that might be built. The source may also be from a rectifying circuit utilizing commercial current or it might be derived from various types of motor generator sets. In the use of motor generator and rectifying equipment it is essential that a smooth non-pulsating current be obtained. Warwick,[18] who originally aroused interest in this method of treatment in this country, advised that his special type of generator, together with a special electrode and a special electrolyte, were necessary for success. The composition of the electrode and the electrolyte were kept secret for a time. However, the informed opinion today holds that the special generator electrode and electrolyte are not essential to success. Any source of smooth galvanic current, ordinary zinc solution, and an ordinary zinc electrode will be effective.[19, 20, 21]

Technique. The technique as ordinarily employed consists in preliminary cocainization of the nasal mucosa. Gauze strips saturated in a 2% solution of zinc sulphate are packed into the nasal chambers. By means of a zinc electrode the gauze is connected to the positive terminal of a galvanic supply. The negative terminal is connected to a large sponge electrode placed over the arm or other suitable portion of the body. The current is slowly turned on and increased until the milliameter reads 10. This amount of current is permitted to act for 15 minutes and the current is then gradually decreased and shut off. Hollender[22] has described a new head band type of electrode that is easy of application and adjustment. Cottle[21] advises the use of a 2% zinc sulphate in 5% tragacanth jelly introduced into the nasal cavities by means of a syringe instead of packing with gauze strips. There is some objection to the use of the jelly in that it spreads to the upper portions of the nose so as to affect the Schneiderian membrane with the possibility of a resulting anosmia, which has occurred. At termination of the treatment the mucous membrane will be found to have been coated with a gray membrane. On the following days the nose is obstructed with a fibrinous jelly-like exudate which persists from 3 days to 1 week. The membrane should be permitted to be extruded spontaneously.

Tissue Changes in Iontophoresis. There is an increasing amount of study upon the effect of iontophoresis upon the treated tissue. There, however, is as yet no certain agreement as to the amount and permanence of tissue change subjected to ionization. Hollender and Gorin[23] find that there is an initial destruction of the surface epithelium with subsequent regeneration. The regenerated mucosa appears first as a squamous epithelium and then gradually assumes a pseudo-stratified structure within a period of 3 months. The cilia, however, remain absent while the subepithelial stroma tends to become more dense and infiltrated with lymphocytes that may persist for a much longer period of time. In but one section were they able to observe changes in the mucous glands. McMahon[24] stated that in the frontal sinuses and nose of dogs subjected to experimental ionization there appeared immediately after the treatment fragmentation of individual and large groups of cells and an infiltration of round cells from the surface down into the subepithelial structures. There was also apparent some separation of the tissue from the underlying periosteum in places. There was a return, however, within a period of 7 weeks of the epithelium to normal. Fibrosis of the subepithelial tissues became more noticeable as the animals were killed in increasing intervals from 18 hours to 7 weeks following the iontophoresis. In a report[25] made by the same investigator in a previous year there was found extensive immediate effects that were definitely destructive, in the nature of ballooning, fragmentation and loss of the surface epithelium associated with edema and partial disintegration of the subepithelial tissues as well as hemorrhagic extravasation from dilated and ruptured capillaries. In an extensive study of the regeneration of the nasal mucosa subjected to various insults, Boling[26] found that ionization destroyed the epithelium and produced leukocytosis and hyperemia; but had no noticeable effect upon the regeneration of the mucosa. The epithelium and glandular ducts regenerated from the basal cells and epithelial fragments left after the treatment. He also found that repeated ionization had no noticeable destructive effect upon the epithelium which regenerated from a previous ionization.

Smit,[27] in a similar study, found that immediately after ionization there occurred an acute inflammatory process with coagulation necrosis, sloughing of the epithelium, dilatation of the bloodvessels and neutrophil infiltration. These changes form an exudate membrane in the nose which also contains the sloughed epithelium. As the acute process subsides, the neutrophils are replaced by round cells which persist as long as there is any irritative process present. The denuded mucosa later becomes covered by stratified squamous epithelium. A return of normal ciliated epithelium was found to occur in guinea pigs 6 weeks following ionization and in one human biopsy 1 year after treatment. The bloodvessel walls show thickening while the glands and their ducts may evidence atrophy and metaplasia. As the reparative process continues, the submucosa becomes infiltrated with fibroblasts which are later converted to fibrous tissue. The contraction of the fibrous tissue may cause collapse of the venous spaces and retraction of the turbinates. New glands may appear by the ingrowth of epithelium. Cartilaginous necrosis may also occur. From these studies it is obvious

that extensive destruction of tissue is possible by this means of treatment. It is also apparent that there is tremendous regenerative power inherent in the nasal mucosa. The mucosal epithelium apparently has a tendency to return to normal, but the subepithelial fibrosis apparently persists for a long period of time and in addition there may be more or less atrophic changes in the glands.

From the clinical point of view the persistence of a fibrotic condition of the mucosa may not be without deleterious effects upon the patient. A contractile fibrous tissue change might well lead to ultimate decrease of blood supply and glandular atrophy. In addition late effects upon the nerves may eventuate in such unpleasant sequelæ as neuritis and anosmia, which have been observed in some instances. In all probability the intensity and extent of these tissue changes will be found to vary with the strength of the treatment that is administered. The problem is so to select the quality of the treatment as to effect the desired clinical relief without producing the progressive and irreversible histologic changes that might lead to disagreeable sequelæ.

The mechanism whereby relief is obtained following ionization has been the object of considerable speculation. Alexander[28] believes that a local non-specific desensitization occurs similar to that obtained by the use of various chemicals, diathermy, and electric cautery. The nasal mucosa has been found to be non-reacting for a period of time. However, the non-infrequent relief obtained by only treating one side might suggest a general non-specific desensitization such as is observed by the use of proteins or vaccines. That this may be a possibility is demonstrated by Chatjutin,[29] who was able to relieve nasal allergy by calcium ionization applied to the skin of the shoulder. Dean and his co-workers[12] noted many instances of positive reaction in the nasal mucosa to negative after ionization. Operative procedures within the nose had no effect in changing the reactivity of the nasal mucosa. Alexander[28] found that after ionization the topical application of a reagin caused little or no effect, in marked contrast to the effect prior to the treatment. Those patients in whom poor or no results were obtained by the therapy reacted within a short time to testing with reagins. However, the iontophoresis had no effect upon the presence of reagins in the blood nor upon the skin reactions.

The results in this type of therapy are varied. Warwick[18] reported practically 100% benefit in 40 cases, most of which were hay fever. Alden, in 1933,[30] relieved all of 19 patients suffering from autumnal fever by treating them during the attack. Nine had no recurrence during the following season, 8 had mild symptoms that were insufficient to cause them to seek aid and 2 had a marked recurrence. He also treated 41 patients in 1934 prior to the onset of the symptoms with protection to about half. Franklin[31] was able to render 50% of his hay fever patients and 60% of his hyperesthetic rhinitis cases free from symptoms by means of iontophoresis. Hollender[22] secured similar relief in about 50% of his cases. Hurd[20] states that in cases of hay fever his percentage of good results have been high and that 70% of his cases of hyperesthetic rhinitis have been rendered symptom-free. He, however, gives no table of statistics beyond the statement noted. Ramirez[32] was unable to obtain any noteworthy relief in 100 cases of

hay fever treated by ionization. On the other hand, 25 cases of vasomotor rhinitis experienced relief in the majority of cases. House and Gay[33] studied this form of treatment in 20 cases. In 5 non-allergic patients 3 were improved, 1 unimproved and 1 made worse. In 15 allergic patients but 3 were improved, 7 were unimproved and 5 were worse. They concluded that ionization was not worthy of consideration in allergic cases. Alden[34] compiled the results of a number of observers. A total of 700 cases was tabulated. In 416 cases of uncomplicated hay fever, complete relief was obtained in 63% and total failure in but 8%. In a group of 27 patients with asthma, 37% were relieved. In 73 patients with allergic rhinitis complete relief was afforded in 47%. Tobey[35] stated that desensitization was the method of choice although ionization can control the symptoms if instituted after the onset of the attack. It is apparent that ionization is a useful addition to the therapeutic armamentarium. It is also apparent that its exact sphere of utility has not as yet been definitely determined.

Our own experience in the last 2 years has definitely impressed us with the symptomatic relief that may be obtained in about 75% of the cases of hyperesthetic rhinitis that have come under our observation. One may not speak of ionization as a cure for this disorder; but the prolonged palliation that may be obtained certainly bespeaks its usefulness. In hay fever our experience has not been so striking. In but few of our cases, treated prior to the onset of the symptoms, were definitely discernible results obtained. Some better results were manifested in its utilization after symptoms had appeared. Here a few patients were rendered symptom-free; a larger number showed definite amelioration, while the greatest majority experienced little or no relief. Ionization must at the present time be viewed as a valuable adjunct to other accepted methods of treating hyperesthetic rhinitis and to a lesser degree hay fever.

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PHYSIOLOGY

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Studies of the Pituitary of Thyroidectomized Rats.—Isolde T. Zeckwer (Laboratory of Pathology, University of Pennsylvania). When thyroidectomy is performed in young immature rats, histologic changes occur in the pituitary which have been discussed elsewhere. "Thyroidectomy cells" occur which consist of cells containing a large amount of hyalin material. Acidophils are decreased in number. Cretin rat pituitaries contain an abundance of thyrotropic hormone, but when injected into guinea-pigs do not cause as great an increase in absolute weight of the guinea-pig thyroid as do normal rat pituitaries. However, the dwarfed cretin rat has available for each gram of its body weight a little more hormone than the normal rat.

The "thyroidectomy cells" are not castration cells, because the cell granules are different, and because they occur in abundance in pituitaries of male rats in which gonad atrophy has not occurred.

Collin and Hennequin (*Compt. rend. Soc. de biol.*, 121, 81, 1936) have reported that stimulation of the cervical sympathetic nerve in rabbits causes an increase in the acidophil granules in the pituitary, while excision of the superior cervical ganglion causes rapid and nearly complete loss of acidophil granules. Until experiments have been completed to determine whether injury to sympathetics could be a factor in our experiments, interpretation that the decrease in acidophils in cretin rats' pituitaries may account for the stunting of kidney growth and body weight will be regarded as only tentative.

The changes in proportion of cell types in the cretin rat pituitary do not prevent the growth of adrenals and gonads in the male.

The present experiments concern only rats. There are apparently species differences in the reaction of the pituitary to thyroidectomy.

Experimental Efforts to Detect Secretion of Inulin by the Tubule of the Mammalian Kidney.—P. A. Bott, B. B. Westfall, and A. N. Richards (Laboratory of Pharmacology, University of Pennsylvania).

Earlier work by the authors, by Smith and Shannon and by Van Slyke and collaborators has furnished basis for the belief that inulin, injected intravenously into mammals, is excreted by the kidney solely by glomerular filtration. Further evidence concerning the possibility that inulin is in part secreted by the mammalian tubule was desired. In a variety of experiments with dogs and rabbits, inulin was added to blood which flowed through the renal vessels at pressures low enough to prevent glomerular filtration. After varied intervals normal blood containing no inulin was substituted at high pressure and a specimen of urine collected. Only traces of inulin were found in it. In every experiment to the inulin-blood was also added one of those substances which are now believed to be secreted into the urine by the tubule (phenol red, neutral red or diodrast). Each of these was found in the urine in relatively large amounts. Hence under conditions which permit tubular secretion of phenol red and other substances, inulin is not secreted by the mammalian tubule.

On the Nature of Intestinal Absorption of Amino Acids.—RUDOLF HÖBER and JOSEPHINE HÖBER (Laboratory of Physiology, University of Pennsylvania). By a number of investigations it has been established that a good many organic substances—provided that they are lipoid-insoluble—enter cells and tissues the more rapidly, the smaller the volume of their molecules (m.v.). An interesting exception to this rule has been disclosed in comparing the entrance of amino acids into physiologic structures with that of other solutes of similar molecular volume. It appeared that the amino acids pass through the surface of cells and tissues, *e. g.*, the surface of red cells or of muscles, with remarkable slowness.

This striking behavior can be explained on a purely physicochemical basis. Experiments on the diffusion of a number of organic substances across collodion membranes have shown that the amino acids similarly penetrate these artificial membranes at a slower rate than would be concluded from their molecular size. The reason is that the "zwitterions" of the amino acids are strong electric dipoles, which, exerting a pull on the surrounding water dipoles, form a water shell preventing them from moving at the expected higher rate.

Then we became aware of still another irregular behavior of the amino acids when we studied their penetration of the intestinal wall of the rat. However, here the observed rates of absorption have not been found to be too low, but, on the contrary, they are much higher than physicochemically demanded. For instance, in comparing the absorption of some amids differing in their m.v., the intestine reveals the properties of an inert diffusion membrane, where penetration occurs parallel to the diffusibility of the solutes, *e. g.*, succinamid m.v. 126, per cent absorbed 3; lactamid m.v. 98, per cent absorbed 52; acetamid m.v. 69, per cent absorbed 78.

The behavior of amino acids is strikingly different, *e. g.*, the m.v. of alanin and malonamid seem to be nearly the same, 98 and 104, but, due to the shell of water dipoles, the effective volume of alanin is by far the greater. Consequently, one would expect the absorption rate of malonamid to surpass that of alanin. But the opposite is true: alanin per cent absorbed 59, malonamid 26. Or: succinamid m.v. 126, per cent absorbed 9, asparagin m.v. 134, per cent absorbed 46.

On the basis of these and other statements we arrive at the result that, as regards their intestinal absorption, the amino acids are privileged in a similar manner as, according to former experiences, some hexoses are.

Absorption of Glucose from the Human Small Intestine.—W. OSLER ABBOTT, W. G. KARR, and T. GRIER MILLER (Gastro-intestinal Section of the Medical Clinic, Hospital of the University of Pennsylvania). In studying the absorption of simple sugars certain steps in the process have been neglected. One of these is the relationship between the concentration of the glucose in the stomach and that in the intestine. Data are presented to show that, irrespective of the volume or the glucose concentration of the solution ingested, the concentrations found in the jejunum and ileum range from 0 to 5%. This confirms in man observations previously made in animals. The fall in concentration between the gastric cardia and the jejunum has been studied by using two multilumened tubes through which sets of specimens could be simultaneously aspirated from five selected points in the stomach and duodenum at stated intervals. Analyses show a wide range of concentration at these points but rarely more than 5.4% of glucose in specimens from near the ligament of Treitz. Further data show that a very rapid inflow of fluid occurs from the walls of the stomach and duodenum. This in conjunction with the predominantly segmental rather than peristaltic action of the duodenum accounts for the sharp fall in concentration by which the small intestine, even as close as 30 to 40 cm. from a stomach containing strongly hypertonic glucose, is provided with a relatively isotonic solution. Feeling from these studies that the normal glucose concentration of intestinal contents is below 5.4% (isotonic), we made absorption studies in segments of jejunum and ileum isolated by distended balloons. Placing 50 cc. volumes of 0.67 to 5.4% glucose solutions in these segments for 15-minute intervals, then emptying and washing with saline, the amount of glucose absorbed could be determined. The results show that the amount of absorption increases with the concentration.

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